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KIDNEY FUNCTION IN ACUTE DISEASE*

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AND
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NEW YORK

In 1918, Frothingham,[1] writing on kidney function as affected by the acute infectious diseases, raised the question as to whether patients without apparent renal involvement would show disturbed kidney function if subjected to proper tests. To determine this, something more than clinical observation is necessary, as indicated by Morse,[2] in 1922, who, in discussing the correlation of clinical and pathologic findings in nephritis, states his belief that the clinical findings and pathologic anatomy do not agree at all well and that kidney lesions cannot be interpreted in terms of apparent function.

An illustration of this independence of the clinical and pathologic aspect is found in Veil's [3] analysis of congenital cystic kidney, by which he demonstrated that the function may remain normal in all respects in this condition.

Reports appear in the literature of the last ten years concerning unusual findings in sick children which might have found satisfactory explanation if disturbed kidney function could have been demonstrated. Of two children with pyelitis,[4] one died with no adequate cause of death other than asthenia. Perhaps a retention and consequent toxemia from reflex impairment of the kidney will explain the fatal outcome. Another developed complete suppression for a period of five days; positive evidence of kidney dysfunction, as may well be another report [5] relating an unexplained oliguria of five days' duration, without albumin or casts, occurring as a complication of colitis.

In a paper on infection of the kidney pelvis, with rise in temperature and systemic disturbance, Ramsey [6] divided his cases into two

* Received for publication, June 29, 1923.

* From the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University; the Children's Medical Division, Bellevue Hospital, and the Department of Pathology, Bellevue Hospital.

1. Frothingham, Channing: Studies on Renal Function, Arch. Int. Med. **22**:74 (July) 1918.
2. Morse, P. F.: Am. J. M. Sc. **163**:697 (May) 1922.
3. Veil, W. H.: Deutsch. Arch. f. klin. Med. **115**:156, 1914.
4. Freeman, R. G.: Tr. Am. Pediat. Soc., 1919.
5. Freeman, R. G.: Arch. Pediat. **36**:367, 1919.
6. Ramsey: Tr. Am. Pediat. Soc., 1922.

groups: (1) those children who throughout the course of the disease played normally and were evidently not consciously affected, and (2) those children who were plainly sick from the disease. No satisfactory explanation of the difference in these two groups was offered.

These are examples of instances in which incomplete diagnosis may have been due to lack of appreciation of the frequency of kidney embarrassment in acute infections. Our own figures in pyelitis indicate the gravity of this embarrassment.

Evidence of such kidney disturbance has been brought out in Schloss'[7] study of intestinal intoxication in infants, in which he demonstrated a remarkable degree of nitrogen retention existing in cases of intoxication, entirely independent of blood concentration or accompanying primary nephritis. Using a method giving consistently higher figures than that of Folin, he showed that, while the nonprotein nitrogen of normal infants' blood ranged from 23 to 39 mg., in forty-four infants suffering from intoxication, the nonprotein nitrogen ranged from 57 to 232 mg. That the increase in nitrogenous elements of the blood was not due to concentration was shown by the absence of any increased corpuscular volume.

These observations were later confirmed by the work of Schwarz and Kohn.[8]

As further evidence of kidney dysfunction, Schloss found the elimination of phenolsulphonephthalein in thirty children suffering from intoxication to be from 4 to 38 per cent., as compared with from 58 to 94 per cent. in normal infants of the same age.

In the fall of 1920, a child, long treated for cystitis and colitis in other institutions, was admitted to the Children's Medical Division of Bellevue Hospital. The urine was alkaline, and contained pus and albumin. The fluoroscope revealed a large vesicle calculus.

The phenolsulphonephthalein test showed elimination of 13 per cent. the first hour, and of 15 per cent. the second hour. Mosenthal's test showed fixation at medium low level, with small total excretion.

Twenty-eight days after the removal of the stone, the urine was normal. The phenolsulphonephthalein excretion was 45 per cent. the first hour and 30 per cent. the second hour. The Mosenthal test showed no fixation. This case is an example of a number of similar instances of apparent serious inhibition of kidney function which have stimulated our interest in the subject.

In addition to the foregoing evidence of a purely clinical and chemical nature, the work of Councilman,[9] in 1898, is of interest from

7. Schloss, O. M.: Intestinal Intoxication in Infants, Am. J. Dis. Child. **15**:165 (March) 1918.

8. Schwarz, Herman, and Kohn, J. L.: Infant of Low Birth Weight; Its Growth and Development, Am. J. Dis. Child. **31**:291 (March) 1921.

9. Councilman: J. Exper. Med. **3**, 1898.

the point of view of pathology. During a period of two and one half years, he observed and described forty-two cases of acute interstitial nephritis occurring in children who had died of diphtheria, measles, whooping cough, empyemia, pneumonia or meningitis, and who had shown no clinical evidence of kidney damage during life.

If infants suffering from intestinal intoxication show consistently such marked retention as Schloss' figures indicate; if there may be such dysfunction accompanying a pelvis infection as our case of pyelitis gave evidence of, and with such anatomic evidence of actual nephritis in the acute infectious diseases, it seems profitable to attempt to learn something more definite in regard to kidney function in a number of other diseases.

As stated by Morse, the appreciation and management of the individual case must depend on the evaluation of each part of the kidney mechanism. Information obtained from examination of the urine alone is not sufficient for this purpose. The presence of albumin and casts in the urine does not necessarily indicate impaired kidney function, nor is their absence a guarantee of a normally functioning kidney.

BASIS OF AUTHOR'S STUDY

We have therefore undertaken this study of kidney function in acute disease, basing it on the information to be gathered from the phenolsulphonephthalein test; the fixation test as modified by Mosenthal, and a study of the chemistry of the blood.

The Phenolsulphonephthalein Test.—From our findings in the study of kidney function in children with nephritis, it is not possible to generalize about the results of this test, except in cases of acute hemorrhagic nephritis. In these, the output was low in the beginning of the disease and rose gradually, with a concomitant drop to normal of the metabolites in the blood. The output did not become normal, however, for some time, in a few cases months, after all clinical and urinary signs had disappeared, and the blood constituents had become normal.

In the chronic cases, the findings were different, and the blood chemistry findings did not always parallel the results of the phenolsulphonephthalein test. One patient who came to us with a retention in the blood of 111 mg. of nonprotein nitrogen had at that time an output of 5 per cent. This rose gradually to 25 per cent., when the nonprotein nitrogen dropped to 96 mg., with a uric acid of 6.2. After this, the phenolsulphonephthalein output remained at 25 per cent., although the uric acid became normal in amount and the nonprotein nitrogen at one time fell to 45 mg. This child passed enormous quantities of urine, and, in spite of these findings, did very well clinically during the time she was under observation.

In contrast to this case is one in which the patient constantly had a phenolsulphonephthalein output of from 45 to 50 per cent., in spite of nonprotein nitrogen retention varying from 60 to 80 mg., and on only two occasions being as low as from 40 to 45 mg. The uric acid was always from 4 to 5 mg. Another child, who clinically seemed to have a more severe condition, with marked edema and low output of urine, had practically normal metabolites and a phenolsulphonephthalein output usually of from 45 to 70 per cent. It seems then that, in the ordinary case of acute nephritis in childhood, the phenolsulphonephthalein test is a fair index of kidney function and when made repeatedly during the course of the disease gives sufficiently accurate evidence as to the recovery of the kidney. The findings in the chronic cases, on the other hand, lead us to be guarded in basing a prognosis on the results of the phenolsulphonephthalein test, and we feel that the blood chemistry findings are of more value as an indication of the functioning not only of the kidneys but also of the whole body metabolism.

Leopold and Burkhart [10] place the range of phenolsulphonephthalein excretion in normal children at from 50 to 90 per cent., an average of 70 per cent. Tileston and Comfort [11] give an even higher average (80 per cent.).

Over a period of years on the Children's Medical Division, the phenolsulphonephthalein output in normal children averaged 60 per cent.; in the early stages of acute nephritis, 10 per cent., in chronic nephritis 40 per cent. The lowest figure was 5 per cent., the highest, 95 per cent. In thirty-four infections, the output was below 50 per cent. in twenty cases, or 60 per cent. of cases. The average output was 39.3 per cent.

Fixation of Specific Gravity.—In the cases of chronic nephritis, the urine had a low fixation of gravity; i. e., around 1.010. One child who had at first a high fixation, around 1.020 to 1.025, later, in the acute stage, had a normal variation; but finally came back to the hospital as a chronic nephritic. In only 33 per cent. of the cases of acute hemorrhagic nephritis was there a fixation of gravity in the first part of the disease, and this later disappeared. The other patients all had a normal variation from the beginning.

As a method of interpretation of the condition of the kidney function in chronic nephritis, it is of disinct value in children.

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10. Leopold, J. S., and Burkhart, Adolph: Nonprotein Nitrogen Constituents of the Blood and the Phenolsulphonephthalein Test in Children, Am. J. Dis. Child. **11**:432 (June) 1916.

11. Tileston, Wilder, and Comfort, C. W.: Total Nonprotein Nitrogen and the Urea of the Blood, and the Phenolsulphonephthalein Excretion in Children, Am. J. Dis. Child. **10**:278 (Oct.) 1915.

The Chemistry of the Blood.—By this means, the most reliable information is obtained as to the reaction of the kidney to acute infections.

Methods: In determining nonprotein nitrogen, uric acid and creatinin, the system of Folin and Wu was followed.[12] The earlier uric acid determinations were made by Folin's first method; the later ones were made by his modified method, introduced in 1922.[13]

We realize that what is determined as creatinin is possibly not creatinin, but the significance of the color producing substance remains the same. We have put the upper normal limit for creatinin at 2; for nonprotein nitrogen at 35, and for uric acid at 3.5. These limits may seem too low in view of some figures published for adults; but we think that in normal children the levels are constantly lower than in adults. In our studies of nephritis, we found a creatinin of 2 mg. to be of more significance than it would be in an adult.

The group of infections studied includes: thirty cases of pneumonia in patients under 2 years of age; forty cases in patients over 2 years of age; five cases of bronchitis; twelve, pulmonary, glandular and miliary tuberculosis; ten, tuberculous meningitis; eleven, epidemic (lethargic) encephalitis; sixteen, tonsillitis; forty-three, chorea; twenty-six, miscellaneous infections; twelve, postoperative, noninfectious.

Blood chemistry in normal children: In 1917, Meyers and Chapin[14] published figures on the blood chemistry of 149 children. Their values are similar to those obtained in adults, but slightly lower. They conclude that the kidney of the child is more efficient and that nitrogen retention is less quick to develop. Folin's[15] figures in 1922, on twelve young men, were: nonprotein nitrogen, minimum 27.8, maximum 39.4, average 32.1; uric acid, between 0.7 to 3.0. This was found to be subject to great variations normally. Creatinin was remarkably constant, at from 1.2 to 1.5.

Our figures for ninety-one normal children (without evidence of acute infection), aged from 1 month to 13 years, correspond to the foregoing, and are shown in the accompanying table.

If these figures were grouped according to age, the children of 2 years and under would show a slightly lower average for nonprotein nitrogen (about 26 mg.). The figures for uric acid and creatinin would not change materially.

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12. Folin, O., and Wu, H.: J. Biol. Chem. **38**:81 (May) 1919.

13. Folin, O., and Wu, H.: J. Biol. Chem. **54**:2, 1922.

14. Chapin, H. D., and Meyers, U. C.: Chemical Examination of the Blood in Children, Am. J. Dis. Child. **18**:555 (Dec.) 1919.

15. Folin, O., and Wu, H.: Physiol. Rev., 1922.

TABLE 1.—*Ninety-One Normal Cases*

Case	Age	Sex*	Non-protein Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
226	10 yr.	♂	26	1.3	1.2	....	Negative	Well child
227	14 yr.	♀	33	1.4	1.1	....	Negative	Well child
228	3 yr.	♂	30	1.8	...	....	Negative	Well child
229	6 yr.	♂	30	2.6	1.3	....	Negative	Well child
230	8 yr.	♂	27	2.0	...	....	Negative	Well child
231	12 yr.	♀	31	2.1	1.0	....	Negative	Well child
232	10 yr.	♀	32.1	2.0	1.3	....	Negative	Well child
233	14 yr.	♀	28	...	1.5	....	Negative	G. C. vaginitis
234	11 yr.	♀	34	2.0	1.2	....	.....	G. C. vaginitis
235	1 mo.	♂	34	1.5	...	....	.....	G. C. vaginitis
236	5 mo.	♂	28	1.4	1.2	....	.....	G. C. vaginitis
237	4 yr.	♀	30	3.2	...	....	Negative	Epilepsy
238	9 yr.	♂	35	1.6	...	....	Alb., tr.	Epilepsy
239	.....	♂	36	2.6	...	....	Negative	Epilepsy
240	8 yr.	♀	30	2.2	...	....	Negative	Epilepsy
241	7 yr.	♀	21	1.6	...	....	Negative	Epilepsy
242	9 yr.	♂	27	2.2	...	....	Negative	Petit mal
243	8 yr.	♂	27	3.9	...	....	Negative	Epilepsy
244	7 yr.	♂	32	2.6	...	....	Negative	Epilepsy
245	5 yr.	♂	30	...	...	....	Negative	Epilepsy
246	10 yr.	♂	35	3.1	...	....	Negative	Epilepsy
247	9 yr.	♀	27.2	3.2	1.5	....	Negative	Epilepsy
248	1 yr.	♂	31	2.0	1.1	....	Negative	Petit mal
249	5 yr.	♀	21	1.6	...	....	Negative	Epilepsy
250	4 mo.	♂	26	3.6	...	....	Negative	Malnutrition, D.
251	8 mo.		16	0.7	...	....	Alb., tr.	Malnutrition
252	8 mo.	♂	30	1.2	...	....	Negative	Malnutrition
253	10 mo.	♀	23	0.8	...	....	Negative	Malnutrition
254	9 yr.	♀	37	3.0	...	....	Alb., tr.	Dementia praecox
255	11 yr.	♀	30	2.5	...	....	Negative	Tumor of spinal cord
256	1 mo.	♀	25	1.5	1.0	....	.....	Foundling
257	.....	♂	25	1.9	...	....	Negative	Constipation
258	7 yr.	♂	35	3.5	1.5	....	Negative	Constipation
259	10 yr.	♂	30	2.8	...	....	Negative	Constipation
260	4 yr.	♀	30	2.3	1.2	....	Negative	Little's disease
261	7 yr.	♂	..	1.5	...	....	Negative	Idiot
262	8 mo.	♂	31	1.5	1.1	....	.....	Mongol.
263	6 mo.	♂	29	...	...	....	Alb., tr.	Idiot
264	14 mo.	♂	24	2.1	1.1	....	Negative	Idiocy
265	8 yr.	♂	30	2.5	...	....	.....	Scurvy (idiot)
266	7 yr.	♀	28	...	...	....	Negative	Cretin
267	6 yr.	♂	33	2.0	0.8	....	Negative	Cretin
268	1 yr.	♀	29	2.5	...	....	Negative	Cretin
269	8 yr.	♀	31.5	1.0	...	....	Negative	Cretin
270	10 yr.	♀	32.7	2.0	1.0	....	Negative	Cretin
271	4 yr.	♂	30	2.1	1.1	....	Negative	Cretin
272	13 yr.	♀	30	1.0	...	....	Negative	Cretin
273	4 mo.	♀	37	3.3	...	....	.....	Hydrocephalus
274	1 yr.	♂	31	2.3	...	....	Negative	Birth injury
275	9 yr.	♂	27	2.4	...	....	Negative	Hemophilia
276	1 mo.	♂	27	2.4	...	....	Negative	Anemia
277	7 yr.	♂	30	2.1	...	....	Negative	Anemia
278	6 yr.	♂	30	2.4	...	....	Negative	Anemia
279	7 yr.	♀	26	2.5	...	....	Alb., tr.; W.B.C., 1+	Anemia
280	10 yr.	♂	21	2.0	...	....	Negative	Undiagnosed
281	6 yr.	♀	28	2.0	...	....	Negative	Spleen
282	3 yr.	♂	25	1.9	...	....	Negative	Spleen
283	8 yr.	♂	28	2.5	1.2	....	Negative	Obs. for nephritis
284	3 yr.	♂	20	2.5	...	....	Negative	Obs. for nephritis
285	6 yr.	♂	24	2.8	...	....	Negative	Obs. for nephritis
286	11 yr.	♀	26	2.2	1.0	....	Negative	Obs.
287	7 yr.	♂	33	1.8	...	....	Negative	Obs.
288	8 yr.	♀	30	2.6	...	....	Negative	Obs.
289	12 yr.	♀	31	2.6	1.0	....	Negative	Obs.
290	4 yr.	♂	20	1.8	1.1	....	Negative	Obs.
291	4 yr.	♂	30	1.0	...	....	Negative	Obs.
292	11 yr.	♀	29	1.7	1.2	....	Negative	Obs.
293	1 yr.	♂	29	2.6	...	....	Negative	Purpura
294	1 yr.	♂	26	3.8	...	....	Negative	Purpura
295	6 yr.	♂	30	2.4	1.2	....	Alb., tr.	Purpura
296	1 yr.	♂	21	1.4	1.4	....	Negative	Tetany
297	13 mo.	♂	25	1.6	1.0	....	Negative	Tetany

* In this column, ♀ indicates female; ♂, male.

The answer to the entire question with which we are concerned is found in Chart 1, in which the range of nitrogenous constituents found in the examination of blood from ninety-one normal children is compared to that of 217 children with infections of all kinds.

Definite evidence of retention of nonprotein nitrogen, uric acid and creatinin is shown in about one half the cases of infections. There seemed to be no constant individual relationship between the increase of uric acid and of nonprotein nitrogen, but, considering all infections, high uric acid was noted in a greater number of cases than was a high nonprotein nitrogen.

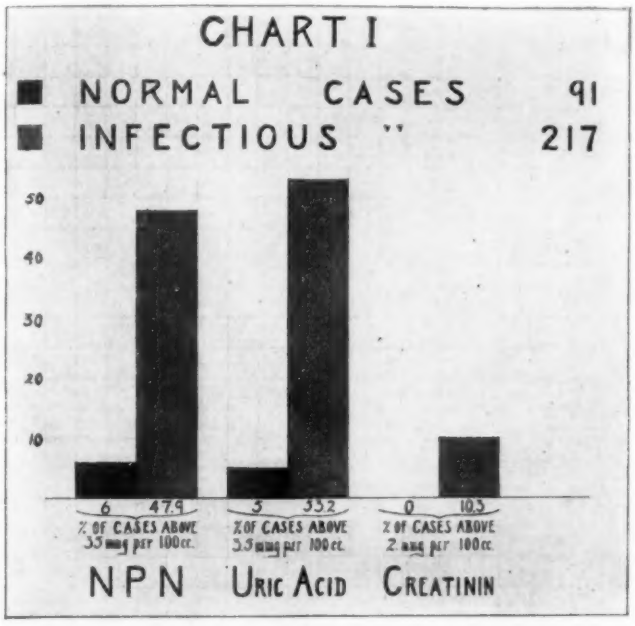

Chart 1.—Comparison of blood chemistry of ninety-one normal children and that of 217 children presenting infections.

INCIDENCE OF RETENTION IN VARIOUS INFECTIONS

Pneumonia.—In seventy cases of pneumonia, the averages and percentage of figures above high normal point plainly toward a definite effect on kidney function in this disease, more pronounced in children over 2 years of age than in those under.

Bronchitis.—Of five cases examined, one showed an increase of nonprotein nitrogen, and two an increase in uric acid.

Tuberculosis (Pulmonary, Glandular and Miliary).—These twelve cases show the same general increase as cases presenting other infec-

TABLE 2.—*Two Hundred and Seventeen Infections*

Case	Age	Sex*	Non-protein Nitrogen	Urea Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
1	3 yr.	♀	42	14	1.8	1.3	....	Alb., h. tr.; pus, 2+	Pyelitis, Imp.
2	11 yr.	♀	40	..	4.0	...	....	Alb., 2+; pus, 44.4	Pyelitis, Imp.
3	3 yr.	♀	22	..	2.2	...	....	Pus, 38%	Pyelitis, Imp.
4	4 yr.	♀	21	..	3.9	...	....	Alb., 2+; sugar, +; pus, 2+	Pyelitis, Imp.
5	.....	♀	49	..	5.7	...	1-30, 2-30 (1/26/23)	Alb., tr.; pus, 2+	Pyelitis, Imp.
6	7 yr.	♀	40.8	..	3.0	...	33	Alb., n. g.; pus, +	Pyelitis, Imp.
7	8 yr.	♂	50	..	4.0	1.4	....	Alb., h. cloud; pus, 4+	Pyelitis, rectal vesicular fistula, C.
8	1½ yr.	♀	22.6	..	5.6	...	....	Alb., cloud; pus, 2+	Pyelitis, rickets, O. M. P. A., Imp.
9	2½ mo.	♀	76	..	10.0	3.0	31.1	Alb., 3+; pus, 3+	Pyelitis, D.
10	.....	..	37.5	..	2.4	...	....	Alb., neg.; pus, 1+	Pyelitis, Imp.
11	3 yr.	♀	29	..	2.1	1.0	1-20, 2-10	Alb., neg.; few W.B.C	Pyelitis, chronic, Imp.
12	3 yr.	♂	30	..	3.6	...	3-44	Alb., tr.; casts; W.B.C.; R.B.C.	Tonsillitis, C.
13	7 yr.	♀	35.2	..	5.6	...	40	Alb., +	Tonsillitis, C.
14	9 yr.	♀	31	..	7.2	...	....	Alb., ft. tr.; W.B.C.	Tonsillitis, C.
15	3 yr.	♂	30	..	4.5	...	....	Alb., 2+	Tonsillitis, C.
16	6 yr.	♂	36	..	5.6	1.8	1, 2-46	Negative	Tonsillitis, C.
17	5 yr.	♂	45	..	3.0	...	....	.....	Tonsilitis, C.
18	5 yr.	♀	39	..	3.2	...	....	Alb., tr.; W.B.C.	Tonsillitis, C.
19	8 yr.	♀	21	..	4.4	...	....	Alb., 2+; W.B.C.; casts	Tonsillitis, C.
20	6 yr.	♀	28	..	7.0	...	....	Not tested	Tonsillitis, C.
21	6 yr.	♂	41	..	2.4	...	....	.....	Tonsillitis, C.
22	4 yr.	♀	28	..	5.0	...	....	Negative	Tonsillitis, C.
23	4 yr.	♂	45	..	6.1	2.0	....	Alb., tr.; W. B. C.	Tonsilitis, C.
24	6 mo.	♀	24	..	1.3	1.2	....	Not tested	Peritonsillar abscess, C.
25	7 yr.	♀	29	..	5.8	...	....	Negative	Tonsillitis, C.
26	3 yr.	♂	22	..	4.0	...	....	Negative	Tonsillitis, C.
27	3 yr.	♂	39	..	4.8	...	1-40	Alb., h. cloud; W.B.C.; casts	Tonsillitis, C.
28	9 yr.	♂	46	..	4.2	1.4	....	Negative	Encephalitis, Imp.
29	3 yr.	♂	34	..	2.1	1.3	....	Negative	Encephalitis, D.
30	8 yr.	♂	39	..	8.0	...	....	Alb., 3+; casts	Encephalitis, Imp.
31	8 yr.	♂	40	..	8.0	...	....	Negative	Encephalitis, Imp.
32	2 yr.	♂	36	..	2.2	...	....	Alb., tr.; W.B.C.	Encephalitis, Imp.
33	11 yr.	♀	46	..	2.7	1.1	....	Neg., 43.1	Encephalitis, Imp.
34	11 yr.	♀	34	..	1.3	1.2	....	Alb., ft. tr.	Encephalitis, Imp.
35	4 yr.	♂	37	..	4.0	1.2	....	Negative	Encephalitis, Imp.
36	7 yr.	♂	36	..	3.5	...	....	Not tested	Encephalitis, Imp.
37	7 yr.	♂	55	..	5.3	...	....	Not tested	Encephalitis, bronchopneumonia, D.
38	6 yr.	♂	31.5	..	3.0	...	....	Negative	Encephalitis, D.
39	3 yr.	♂	30	..	4.5	...	....	Alb., 2+; casts 0	Encephalitis, Imp.
40	10 yr.	♂	35	..	1.8	1.5	....	Negative	Chorea, Imp.
41	10 yr.	♂	28	..	1.4	1.2	....	Negative	Chorea, Imp.
42	11 yr.	♀	27	..	1.7	1.3	....	.....	Chorea, Imp.
43	9 yr.	♀	23	..	1.4	1.2	....	Negative	Chorea, Imp.
44	7 yr.	♀	28	..	1.6	1.3	....	Negative	Chorea, Imp.
45	9 yr.	♀	32	..	2.1	1.4	....	Negative	Chorea, Imp.
46	7 yr.	♀	..	..	2.0	1.1	....	Negative	Chorea, Imp.
47	11 yr.	♀	37	..	3.9	1.4	....	Negative	Chorea, Imp.
48	9 yr.	♂	35	..	3.6	...	....	Negative	Chorea, Imp.
49	12 yr.	♀	43	..	2.6	...	....	Negative	Chorea, cardiac, Imp.
50	8 yr.	♀	27	..	3.6	...	....	Negative	Chorea, Imp.
51	9 yr.	♀	27	..	3.33	2.0	....	Negative	Chorea, con. syphilis, Imp.

* In this column, ♀ indicates female; ♂, male.

TABLE 2.—*Two Hundred and Seventeen Infections—(Continued)*

Case	Age	Sex*	Non-protein Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
52	8 yr.	♂	38	3.26	1.7	....	Negative	Chorea, Imp.
53	8 yr.	♂	31	3.20	...	....	Negative	Chorea, Imp.
54	8 yr.	♂	40	3.63	...	....	Negative	Chorea, Imp.
55	10 yr.	..	35	2.20	1.3	....	Negative	Chorea, Imp.
56	6 yr.	..	28	2.90	1.5	....	Negative	Chorea, Imp.
57	11 yr.	♀	34	2.0	1.2	....	Negative	Chorea, Imp.
58	8 yr.	..	35	1.5	1.1	....	.....	Chorea, Imp.
59	10 yr.	♂	48	5.	...	....	Negative	Chorea, Imp.
60	7 yr.	♂	34.5	3.7	1.2	35, 25	Negative	Chorea, Imp.
61	12 yr.	♂	31.2	2.5	...	....	Negative	Chorea, Imp.
62	6 yr.	♂	42.6	2.1	...	....	Negative	Chorea, Imp.
63	10 yr.	♀	35	1.3	...	....	.....	Chorea, Imp.
64	9 yr.	♂	30	2.4	...	....	Negative	Chorea, cardiac, Imp.
65	6 yr.	♀	40	3.6	...	....	.....	Chorea, Imp.
66	9 yr.	♀	46	3.7	...	....	Negative	Chorea, Imp.
67	9 yr.	♂	31	3.0	...	....	Negative	Chorea, Imp.
68	12 yr.	♀	30	3.2	...	....	Alb., tr.; W.B.C.	Chorea, Imp.
69	10 yr.	♂	39	2.5	...	....	.....	Chorea, Imp.
70	10 yr.	♀	36.6	3.0	...	....	Negative	Chorea, Imp.
71	12 yr.	♂	50	3.0	...	....	.....	Chorea, cardiac, Imp.
72	11 yr.	♂	25	4.6	...	....	Negative	Chorea, Imp.
73	9 yr.	♀	29.5	4.8	...	....	Negative	Chorea, Imp.
74	.....	♀	35.2	2.5	...	....	Negative	Chorea, Imp.
75	11 yr.	♂	46	2.9	...	....	Negative	Chorea, Imp.
76	11 yr.	♂	43.8	2.3	...	....	Negative	Chorea, cardiac, Imp.
77	5 yr.	♀	26.3	2.1	...	....	Negative	Chorea, cardiac, Imp.
78	5 yr.	♂	36.6	2.8	...	....	Negative	Chorea, Imp.
79	8 yr.	♀	40	2.7	...	....	Alb., tr.	Chorea, Imp.
80	10 yr.	♀	41	4.2	...	....	Negative	Chorea, cardiac, Imp.
81	7 yr.	♀	44	3.0	...	....	Negative	Chorea, cardiac, Imp.
82	8 yr.	♀	35.2	7.2	...	....	Alb., tr.	Chorea, cardiac, Imp.
83	9 yr.	♂	37.5	3.5	...	....	Negative	Chorea, Imp.
84	2 yr.	♂	40	3.6	...	....	Alb., 2+; sug. 2+	Tuberculous meningitis, D.
85	3 yr.	♂	102	6.6	...	....	.....	Tuberculous meningitis, D.
86	2 yr.	♀	38	3.8	1.7	....	Alb., 2+	Tuberculous meningitis, D.
87	7 yr.	♂	43	3.0	1.4	. ..	Alb., tr.	Tuberculous meningitis, D.
88	1 yr.	♂	76	...	...	....	Negative	Tuberculous meningitis, D.
89	2 yr.	♀	91	5.0	2.1	....	Not tested	Tuberculous meningitis, D.
90	12 yr.	♂	46	2.7	1.4	....	Alb., casts	Tuberculous meningitis, D.
91	2 yr.	♂	44	6.2	..	....	Alb.; W.B.C., 42 8%	Tuberculous meningitis, D.
92	.....	♂	85	9.4	1.7	....	Not tested	Tuberculous meningitis, D.
93	1 yr.	♀	35	2.0	...	....	Negative	Tuberculous meningitis, D.
94	3 yr.	♂	32	3.7	...	2 hr., 45	Negative	Acute bronchitis, C.
95	5 yr.	♂	19	3.0	...	....	Negative	Acute bronchitis, C.
96	6 yr.	♂	30	1.0	...	....	Negative	Acute bronchitis, rickets, C.
97	1 yr.	♂	41.1	4.0	...	....	Negative	O. M. P. A., anemia, C.
98	.....	♂	27	3.4	...	....	.....	Chronic bronchitis, C.
99	11 yr.	♂	39	4.0	1.4	....	?	Pulmonary tuberculosis (?)
100	9 mo.	♂	33	4.0	...	....	?	Pulmonary tuberculosis, D.
101	10 yr.	♀	41	3.2	1.4	1-30, 2-25	Alb., ft. tr.	Pulmonary tube., Imp.
102	4 yr.	♀	30	2.5	...	....	Negative	Pul. tbc., N. A. O. R., Imp.
103	3 yr.	♀	44	3.0	1.4	...	Negative	Pulmonary tube., Imp.
104	6 yr.	♂	22	3.6	...	41	Negative	Pulmonary tuberculosis, U.
105	10 yr.	♀	26	1.5	...	29.6	Negative	Pulmonary tuberculosis, U.
106	2 yr.	♀	20	4.0	...	....	Negative	Tbc. cerv. nodes phlyct. conjunc., Imp.
107	18 mo.	♀	24	7.4	1.1	....	Negative	Tbc. cerv. nodes phlyct. conjunc., A. O. R.
108	1 yr.	♂	31	4.0	...	....	Negative ?	Tbc. cerv. nodes, Imp.
109	3 yr.	♂	36	4.0	...	....	Negative	Miliary tuberculosis, D.
110	9 mo.	♂	38	4.5	...	....	Alb., 5%; W.B.C.	Miliary tuberculosis, D.
111	1 yr.	♂	27	1.7	1.2	....	Negative	Rickets
112	6 mo.	♀	27	1.0	1.3	....	.....	Rickets, tetany
113	6 mo.	♂	22	1.3	1.2	....	.....	Rickets, tetany
114	5 mo.	♀	26	...	...	....	W.B.C.	Rickets, tetany
115	4 mo.	♂	29	3.5	1.3	....	.....	Rickets
116	8 mo.	♂	30	2.5	...	....	Negative	Rickets
117	10 mo.	♂	20	2.3	...	....	Negative	Rickets
118	2 yr.	♂	25	2.7	...	....	.....	Rickets
119	4 mo.	♂	31.5	2.0	1.2	....	Negative	Rickets
120	6 mo.	♀	19	3.2	...	....	Negative	Rickets
121	1 yr.	♂	30	2.0	...	....	Negative	Rickets
122	2 yr.	♂	20	2.0	...	....	Negative	Congen. deformity of hands and feet
123	4 yr.	♂	27	2.6	...	....	Negative	Mental deficiency
124	7 yr.	♂	26.7	1.0	1.3	....	Negative	Chondrodystrophy

* In this column, ♀ indicates female; ♂, male.

TABLE 2.—*Two Hundred and Seventeen Infections—(Continued)*

Case	Age	Sex*	Non-protein Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
125	12 yr.	♂	30	2.0	...	....	Negative	Club foot
126	8 yr.	♂	39	2.0	1.4	....	Negative	Fractured humerus 1 week postoperative
127	6 yr.	♂	33	2.0	1.0	....	Negative	Contracture
128	3 mo.	♂	23.5	3.0	...	....	Negative	Diet regulation
129	13 yr.	♂	30	3.0	1.0	....	Negative	Chlorosis
130	2 yr.	♂	35	1.3	...	....	.....	Diphtheria, C.
131	2 yr.	♂	37	7.2	2.0	....	.....	Diphtheria, cerv. abscess, Imp.
132	4 yr.	♂	32	1.4	1.4	....	.....	Diphtheria, Imp.
133	9 mo.	♀	31	3.0	1.7	....	Not tested	Whooping cough, Imp.
134	6 mo.	♀	32	1.7	1.4	....	.....	Measles, C.
135	4 yr.	♂	34	4.1	...	....	.....	Poliomyelitis, Imp.
136	8 mo.	♂	40	3.0	...	....	Alb., W.B.C.	Furunculosis, Imp.
137	2 mo.	♂	24	1.0	...	....	Alb., +; sug., +	Furunculosis, O. M. P. A., Imp.
138	3 mo.	♀	35	2.3	...	....	Not tested	Furunculosis, C.
139	7 mo.	♂	30	6.5	2.7	....	Alb., +; sug., 2+; pus, +; casts	Eczema furunculosis, AOR
140	9 yr.	♀	34	3.1	...	....	Not tested	Typhoid, C.
141	10 yr.	♂	28	0.7	...	....	Negative ?	Typhoid, C.
142	2 yr.	♀	33	3.7	...	....	Alb., +	Typhoid, C.
143	18 mo.	♀	18	5.0	...	....	Alb., +; W.B.C.	Ac. cholangitis, Imp.
144	4 yr.	♀	31	4.6	...	....	Negative, 41%	Ac. cholangitis, Imp.
145	8 yr.	♂	30	6.0	...	....	.....	Ac. cholangitis, Imp.
146	8 yr.	♂	34	1.2	1.0	....	Negative	Ac. rheum. fever, Imp.
147	4 yr.	♀	25	2.6	...	....	Negative	Ac. rheum. fever, C.
148	2 yr.	♂	49.8	2.0	1.4	....	Negative	Eczema, Imp.
149	1 yr.	♂	42	8.2	...	....	37%	Pemphigus, D.
150	4 yr.	♀	28	6.8	...	....	Alb., tr.	Epidem. meningitis, C.
151	4 yr.	♂	29.5	4.0	...	....	Negative	Chronic epidem. meningitis, hydro., D.
152	9 yr.	♀	30	5.4	...	1-20, 2-5	Alb., N.; pus, +	Stomatitis, C.
153	10 yr.	♂	40	3.6	1.4	....	Alb., 2+; casts	Septicemia, Imp.
154	3 yr.	♂	27	5.3	1.2	2-55	.....	Scarlet fever, Imp.
155	1½ yr.	♂	40	3.0	...	....	.....	Chr. meningitis, Imp.
156	2 yr.	♂	22	2.1	...	....	Negative	Lob. pn., rickets, Imp.
157	1 yr.	♂	23	2.5	1.9	1-45	Alb., ft. tr.; W.B.C.	Lob. pn., rickets, Imp.
158	10 mo.	♀	30.4	5.4	...	....	Negative	Lob. pn., anemia, C.
159	6 mo.	♀	30	7.0	...	....	Not tested	Lob. pn., microceph., D.
160	18 mo.	♀	22	4.1	2.7	....	Alb., 2+	Lob. pn., O. M. P. A., pyelitis, rickets, D.
161	8 mo.	♂	30	2.5	...	....	Alb., 2+; W.B.C.	Lob. pn., D. M. P. A., C.
162	17 mo.	♀	26	3.3	...	....	.....	Lob. pn., O. M. P. A., C.
163	17 mo.	♂	20	2.3	...	....	Negative	Lob. pn., O. M. P. A., C.
164	2 yr.	♂	32	1.8	1.4	....	Negative	Lob. pn., O. M. P. A., C.
165	5 mo.	♂	30	5.4	...	....	Negative	Lob. pn., O. M. P. A., D.
166	15 mo.	♂	33	2.6	1.3	....	.....	Lob. pn., effusion, Imp.
167	2 yr.	♂	53	2.4	1.6	....	Negative	Lob. pn., mastoid, D.
168	15 mo.	♂	39	1.8	...	....	Alb., +; casts	Lob. pn., O. M. P. A., D.
169	14 mo.	♀	38	1.3	1.5	....	Negative	Lob. pn., O. M. P. A., D.
170	1 yr.	♀	26.1	4.0	...	....	Alb., tr.; W.B.C.	Br. pn., rickets, D.
171	1 yr.	♀	40.8	5.3	...	....	Not tested	Br. pn., rickets, D.
172	1 yr.	♀	22	2.4	...	....	Negative	Br. pn., O. M. P. A., C.
173	6 mo.	♂	41	4.0	...	....	Alb., h. cloud; W.B.C.; casts	Br. pn., O. M. P. A., C.
174	1 yr.	♀	38.7	4.0	...	....	Not tested	Br. pn., W. C., D.
175	3 mo.	♂	35.2	4.0	1.0	....	Not tested	Br. pn., D.
176	9 mo.	♂	43	5.5	...	....	.....	Br. pn., necropsy showed cloudy swelling
177	16 mo.	♂	52.5	6.8	...	....	Negative	Br. pn., scurvy, con. heart condition, A. O. R.
178	9 mo.	♂	15	5.3	...	....	Alb., N.; sug., 2+; mx., N.	Br. pn., D.
179	2 yr.	♂	34	1.1	...	....	Negative	Br. pn., O. M. P. A., W. C., D.
180	6 mo.	♂	37	11.4	...	....	Alb., tr.	Br. pn., O. M. P. A., D.
181	7 mo.	♂	26	1.8	...	....	.....	Br. pn., O. M. P. A., D.
182	1 yr.	♂	27	1.4	1.2	....	Negative	Br. pn., O. M. P. A., D.
183	9 mo.	♀	20	2.3	...	....	Negative	Br. pn., O. M. P. A., Imp.
184	2 yr.	?	29	1.9	...	....	Negative	Br. pn., rickets, A. O. R.
185	1½ yr.	♀	30	3.0	1.6	....	Negative	Flu., br. pn., D.
186	9 yr.	♂	26.6	3.0	...	1-15, 2-35	Negative	Lob. pn., C.
187	8 yr.	♂	36	5.6	1.2	1-25, 2	W.B.C.; Grm.; Alb., N.; casts	Lob. pn., C.

* In this column, ♀ indicates female; ♂, male.

TABLE 2.—*Two Hundred and Seventeen Infections—(Continued)*

Case	Age	Sex*	Non-protein Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
188	7 yr.	♂	29	3.6	...	1, 2-35	Negative	Lob. pn., C.
189	9 yr.	♂♀	38	2.5	...	....	Alb., N.; W.B.C., +	Lob. pn., C.
190	3 yr.	♂	60	5.2	1.8	Anuria 24 hr.	Alb., h. tr.; casts	Lob. pn., O. M. P. A., Imp.
191	6 yr.	♂	40	5.2	1.4	2-42	Alb., h. cloud; mx., neg.	Lob. pn., C.
192	3 yr.	♂	39	4.8	1.2	1-40, 2	Alb., h. cloud; W.B.C.; gram casts	Lob. pn., C.
193	11 yr.	♂♀	33.5	3.4	...	1-25, 2-15	Negative	Lobar pn., C.
194	8 yr.	♂♀	27	4.3	1.5	1-55, 2-10	Negative	Lobar pn., C.
195	6 yr.	♀	37	4.0	1.5	1-60, 2-25	Alb., cloud; neg. gram casts	Lobar pn., C.
196	3 yr.	♀	25.2	7.2	...	....	Alb., N.; W.B.C.	Lobar pn., D.
197	3 yr.	♂	22	1.0	...	....	Alb., 2+; casts;	Lobar pn., C.
198	3 yr.	♂♂	28	1.4	1.2	....	Alb., 1+	Lobar pn., C.
199	3 yr.	♂♀	44	1.3	1.4	....	.....	Lobar pn.
200	6 yr.	♂♀	25	6.3	...	....	Negative	Lobar pn., C.
201	7 yr.	♀	46	4.7	1.7	45	Alb., tr.; casts; W.B.C.	Lobar pn., C.
202	3 yr.	♂	26	4.5	1.4	40	Alb., tr.	Lobar pn., C.
203	5 yr.	♂♂	46	5.2	1.6	....	.....	Lobar pn., D.
204	9 yr	♂♂	30	1.7	1.3	35	Negative	Lobar pn., C.
205	8 yr.	♀	42	5.2	1.6	....	.....	Lobar pn., D.
206	.....	..	27	4.7	2.2	....	Alb., tr.; W.B.C.	Lobar pn., O. M. P. A., C.
207	2 yr.	♂	22	4.2	...	....	Negative	Lobar pn., I.
208	6 yr.	♂♂	34	5.7	1.6	....	Negative	
209	8 yr.	♂♀	37	3.6	1.7	1-15, 2-12	.....	Lobar pn , I.
210	7 yr.	♂♂	30	4.0	...	1-33, 2-17	.....	Lobar pn., I.
211	3 yr.	♂♀	44	1.2	1.5	....	.....	Lobar pn., C.
212	8 yr.	♂♀	48	3.3	1.5	45	.....	Lobar pn., I.
213	4 yr.	♂	35	4.4	...	....	Neg., 42.6%	Lobar pn., C.
214	.....	..	28	1.7	1.9	....	Negative	Lobar pn., O. M. P. A., I.
215	4 yr.	♂♂	46	3.2	...	....	Alb., tr.	Lobar pn., I.
216	7 yr.	♂♀	48	6.0	1.7	....	Not tested	Lobar pn., D.
217	6 yr.	♂♀	40	4.5	2.1	....	Alb., tr.	Lobar diph., C.
218	10 yr.	♀	28	3.4	...	....	Negative	Cardiac lobar pn., G. C. vaginitis, D.
219	5 yr.	♂	20.6	4.8	...	2-5	Alb., N.; W.B.C., 2+	Br. pn., D.
220	8 yr.	♀	28	3.8	...	30	Alb., 1+	Br. pn., ac. rheum., F.
221	2 yr.	♂♀	33	1.0	1.5	....	.....	Br. pn., measles, C.
222	4 yr.	♂♀	28	5.6	...	....	Neg., 32%	Br. pn., O. M. P. A., I.
223	3 yr.	♂♀	35	3.0	1.5	....	Alb., N.; W.B.C.	Br. pn., O. M. P. A., I.
224	8 yr.	♂	27.1	5.0	1.2	....	Alb., tr.; W.B.C.	Lobar pn., C.
225	2½ yr.	♀	31	7.0	...	....	Alb., tr.; W.B.C.	Br. pn., D.
298	12 yr.	♂	25.5	3.1	1.1	1-30, 2-20	.....	Contracture fingers, 24 hr. postoperative
299	12 yr.	♂♀	34.5	2.0	1.2	1-40, 2-20	.....	Contracture, 7 days postop.
300	11 yr.	♀	30	5.3	1.2	1, 2-50	.....	Contracture fingers, 24 hr. postoperative
301	11 yr.	♀	30	2.8	1.1	1-20,2-22.5	.....	Contracture, 1 wk. postop.
302	6 yr.	♂♂	31	3.0	1.1	1-50, 2-5	.....	Web fingers, 24 hr. postop.
303	6 yr.	♂♂	33	2.4	1.0	....	.....	Web fingers, 1 wk. postop.
304	10 yr.	♂♂	29	4.4	1.2	1-10, 2-5	Negative	Ing. hernia, 24 hr. postop.
305	10 yr.	♂♂	41.6	3.4	1.2	....	.....	Ing. hernia, 1 wk. postop.
306	7 yr.	♂♂	30	3.8	1.0	1-40, 2-20	.....	Ing. hernia, 24 hr. postop.
307	7 yr.	♂♂	33	2.3	1.1	....	.....	Ing. hernia, 1 wk. postop.
308	3 yr.	♂♂	37.5	8.8	1.6	1-25, 2-15	Negative	Ing. hernia, 24 hr. postop.
309	3 yr.	♂♂	28.5	2.3	1.1	....	.....	Ing. hernia, 1 wk. postop.
310	11 yr.	♂♂	33.3	2.6	1.0	1-5, 2-30	.....	Ing. hernia, 24 hr. postop.
311	11 yr.	♂♂	37.5	2.0	1.0	1-20,2-12.5	.....	Ing. hernia, 1 wk. postop.
312	4½ yr.	♂♂	35.2	6.1	1.5	....	.....	Ing. hernia, 24 hr. postop.
313	4½ yr.	♂♂	21	1.0	1.0	....	.....	Ing. hernia, 1 wk. postop.
314	7 mo.	♂♂	26	5.0	1.8	1-50, 2-30	.....	Ing. hernia, 24 hr. postop.
315	7 mo.	♂♂	20.7	3.0	1.0	....	.....	Ing. hernia, 1 wk. postop.
316	10 yr.	♂♂	42.6	5.2	...	1-15, 2-25	.....	Ing. hernia, 48 hr. postop.
317	10 yr.	♂♂	26.6	2.7	...	....	.....	Ing. hernia, 1 wk. postop.
318	6 yr.	♂♀	37.5	3.7	1.5	1-50, 2-10	.....	Skin graft, 24 hr. postop.
319	6 yr.	♂♀	30.8	2.2	1.0	1-50, 2-10	.....	Skin graft, 1 wk. postop.
320	5 wk.	♀	54.5	8.0	1.4	....	.....	Gastrotomy, 24 hr. postop.
321	5 wk.	♀	30	2.0	1.0	....	.....	Gastrotomy, 8 days postop.

* In this column, ♀ indicates female; ♂, male.

tions, the uric acid being increased in a higher percentage of cases than is the nonprotein nitrogen.

Tuberculous Meningitis.—In the ten cases, the retention is more pronounced in these cases, as one would expect in so severe an infection. This is one of the groups in which the nonprotein nitrogen is increased in a higher percentage of cases than is the uric acid.

Epidemic (Lethargic) Encephalitis.—In the twelve cases, there is a greater number of high nonprotein nitrogen values than of high uric acid values.

Tonsillitis.—In the sixteen cases in this group, an increase in nonprotein nitrogen in 43 per cent. of the cases and of uric acid in 75 per cent. of the cases shows very well the selective action of the kidney. Tonsillitis is accepted as being of especial etiologic importance, or at least as a frequent precedent condition in nephritis, and the type of retention corresponds to that of nephritis.

Pyelitis.—In the eleven cases, the patients who were sick showed retention and those that were not definitely sick had no retention. The degree of retention followed closely the clinical evidences of the severity of the infection.

Chorea.—In forty-three cases of chorea, the nonprotein nitrogen was up in 58.1 per cent. of the number, while the uric acid was high in only 30.2 per cent. Chorea is considered by some as an infection, though it usually runs an afebrile course. The rise in the nonprotein nitrogen level may not be a retention, for the urinary findings are consistently negative, and phenolsulphonephthalein tests made in chorea cases in the last few years have always shown a normal output.

Miscellaneous Infections.—This group of twenty-six cases shows in general the same changes that the other cases of acute infections show.

Surgical Conditions, Noninfectious.—Blood was taken within twenty-four hours after operation in selected clean cases.[16] These patients showed about the same degree of retention as those having acute infections. Phenolsulphonephthalein tests made in ten cases at the same time blood was taken showed a low output (below 50) in four, or 40 per cent. It is interesting to see what effect a combination of shock and anesthesia can have on kidney function. Blood taken one week after operation gave normal findings in practically all of the cases.

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16. These cases became available for test through the kindness of Dr. Carl Burdick, Children's Surgical Division, Bellevue Hospital.

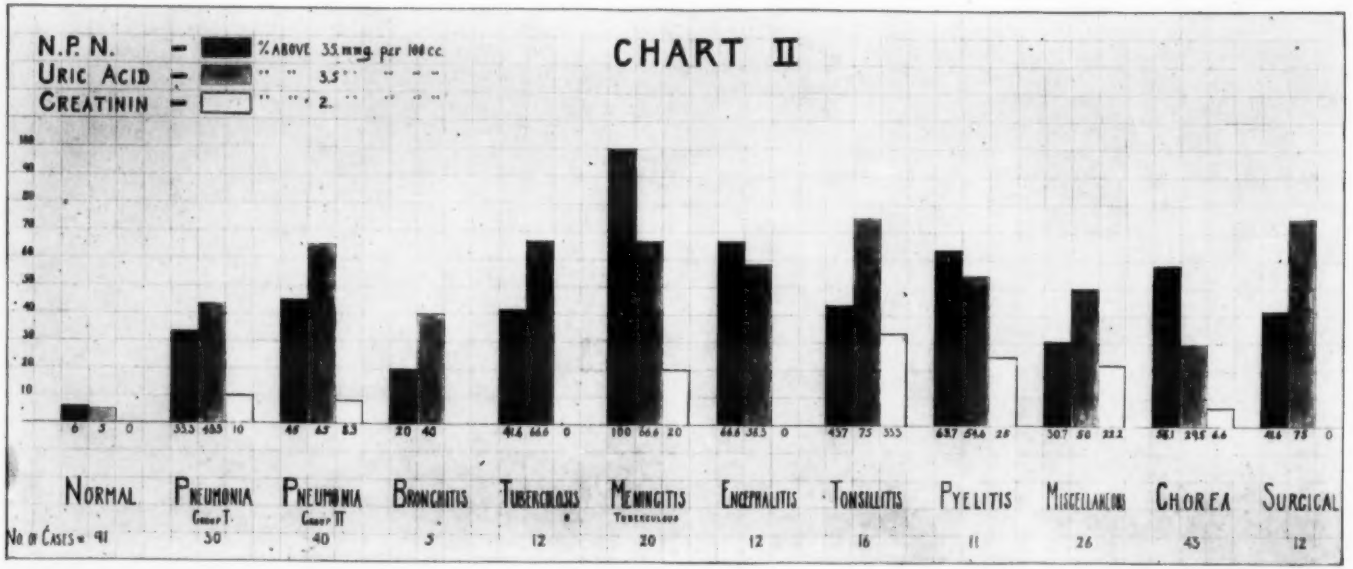

Chart 2.—Percentage increase of nonprotein nitrogen, uric acid and creatinin in 217 infections grouped according to disease.

COMMENT

Mosenthal[17] has shown that in adults the picture of functional impairment found in severe acute nephritis is produced by other conditions, such as pyelitis, cystitis, anemia and diabetes.

The treatment of any of these conditions would certainly be modified if we were aware of the degree to which the kidney function was being hampered by the primary condition, or, conversely, how much such an unrecognized kidney deficiency might be hindering progress.

We do not mean to say that every acute or chronic infection or affection must be subjected to an annoying and expensive series of functional tests, but it should be borne in mind that additional trouble from poor kidney elimination is a possible source of complication, and attention to the kidney function is as important as attention to the action of the intestinal tract. The figures shown in Chart 1 are a basis for this attitude, as there was definite increase in the nitrogen constituents of the blood in about 50 per cent. This could not be attributed to blood concentration because all the hematocrit readings taken were within normal limits, most of them being at about 35 per cent., and none over 45 per cent.

It is also probable that in infection there is toxic destruction of protein; but, normally, the kidney could take care of any increase in waste products from this source. Coleman and Du Bois demonstrated a toxic destruction of protein in typhoid. We have blood chemistry findings in the cases of three children with this disease. They are all well within normal limits except one with a uric acid of 3.7.

It is difficult to decide whether these evidences of nitrogen retention are to be interpreted as due to functional disturbance simply or to actual early nephritis.

Examination of the urine revealed signs of kidney irritation in only half the cases. Less confidence is felt in this evidence because, unfortunately, routine ward analyses were depended on, and therefore there exists certain inaccuracy and incompleteness common to every such procedure.

We were unable to demonstrate any constant relation between blood chemistry on the one hand and urinary analysis or functional tests on the other. Blood retention was associated with normal urine: low phenolsulphonephthalein excretion, with normal blood chemistry; albumin, casts and white blood cells (in urine) with normal blood chemistry and phenolsulphonephthalein excretion.

Comparable to this lack of consistency in these functional tests of kidney competency are the variations found in retention of all elements

17. Mosenthal, H. O., and Richards, A. E.: Interpretation of a Positive Nitrogen Balance in Nephritis, Arch. Int. Med. **17**:329 (Feb.) 1916.

of nonprotein nitrogen, and in a seemingly selective action on certain of them.

Myers [18] and others have long contended that, in the early stages of renal insufficiency, the uric acid is the first nitrogen constituent to be retained, and that in the absence of gout a rise in uric acid in the blood signifies a mild impairment of kidney function; or, in other words, uric acid accumulation precedes and exceeds that of nonprotein nitrogen in the early stages of nephritis.

Folin [19] notes that in gout it is the only substance increased, and asks whether "this is to be interpreted in terms of a highly selective activity and correspondingly selective deterioration of the kidneys, or does it mean that uric acid is more difficult to excrete than any other waste product, a possibility suggested by the high normal levels and by excessive variation in uric acid content of blood of normal persons." In nephritis leading to uremia and in advanced cases of nitrogen retention, there is no constant relationship between increase in nonprotein nitrogen and uric acid, and the latter seldom shows a greater percentage increase than does nonprotein nitrogen. On the contrary, the uric acid accumulation is usually less pronounced.

Foster [20] thinks that, in the early stages, the kidney is intolerant of certain substances, and as the disease progresses, the kidney becomes more tolerant.

Our figures seem to support the view that increase of uric acid is significant of actual early kidney impairment rather than simply dysfunction. Retention does not progress equally as regards the various constituents of nonprotein nitrogen.

Taking the infections as a whole, the difference is not marked, 48 per cent. showing an increase in nonprotein nitrogen, as against 53 per cent. showing an increase in uric acid. But tonsillitis, pneumonia, tuberculosis and the miscellaneous infections show a greater number with high uric acid than with high nonprotein nitrogen retention, the relation being about 60 to 40 per cent.

Estimation of disturbed relation between fluid intake and output is as worthy of observation in any acute condition as is the routine observation of the intestinal function. From it, evidence of faulty fluid elimination may be obtained before actual signs of retention have appeared; and with it in mind, a better estimate of slight early variations in the chemical composition of the blood is possible.

Foster [20] emphasizes the importance of this consideration of fluid balance and retention in the blood. He states that the amount of nitro-

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18. Myers, U. C.; Fine, M. S., and Lough, W. G.: Blood in Nephritis, Arch. Int. Med. **17**:570 (April) 1916.
19. Folin, O.: Physiol. Rev. **2**:460 (July) 1922.
20. Foster, Harvey Lectures, 1921.

gen excretion in the urine bears a relation to the volume of urine, and gives experimental confirmation of a well established clinical doctrine; namely, that these cases of chronic nephritis with nitrogen retention require much water in order to eliminate the nitrogenous waste, because the diseased kidney can excrete only at a low level of concentration of urea.

Pepper [21] stresses the influence of oliguria on nitrogen excretion and blood retention, and believes that nitrogen retention may depend entirely on failure of water elimination without impairment of the urea excreting function of the kidney.

There were forty-three deaths in the series of infections. Of these, 83.7 per cent. showed a retention of one or more of the nitrogenous waste products, as opposed to 50 per cent. of the total infections investigated.

CONCLUSIONS

1. In a series of 217 acute infections (including twelve postoperative noninfections), retention of nitrogenous waste products was shown in about one half of the cases.

2. This retention is thought to be due to simple impairment or depression of kidney function, though in some groups of cases the possibility of nephritis could not be ruled out.

3. Of the three nitrogenous waste products studied, nonprotein nitrogen, uric acid and creatinin, the uric acid was above normal in a greater number of cases than were nonprotein nitrogen and creatinin. This selective retention is shown especially well in the group of twenty-six miscellaneous infections, seventy cases of pneumonia and sixteen cases of tonsillitis. The type and degree of retention in these groups makes one think that possibly we are dealing with early but definite acute nephritis.

4. In some textbooks, no mention is made of kidney function, although many pages are devoted to diet and general hygiene in the treatment of acute infections. Others state that evidences of serious renal impairment are seldom found in early life.

It is clear from the evidence that, in many cases of acute infection, there is definite impairment of kidney function which may not be evident clinically. Certain of these cases may go on to actual nephritis. Emphasis is therefore laid on the necessity for more careful consideration of the kidney in all acute infections and its routine protection from all unnecessary strain.

In some cases, prevention of impending kidney breakdown will thus be provided for; in others, treatment directed at the kidney will be instituted at an early rather than at a late date.

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21. Pepper, O. H. P.: Am. J. Med. Sc. **165**:81 (Jan.) 1923.

REFLEXES OF THE NEW-BORN*

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The study of the reflexes of the new-born has not led until now to exact conclusions as to their mode of action or pathognomonic importance. The various researches on the reflexes, and especially on the most important of them, the plantar and knee reflexes, often give contradictory results as to their mode of action and frequency. Therefore, I think that a summary of results which I obtained from a careful examination of new-born children in the first week of life will be of interest.

The imperfect development of the nervous system in the new-born, due to the embryonal type of ganglionic cells, especially the pyramidal ones, and to the myelinization deficiency, especially in the fibers of the brain, alters all nervous functions; and exact knowledge of these variations from the normal is necessary for the differentiation of physiologic from pathologic phenomena. The younger the child the more important this knowledge is.

As there are no important and clear clinical signs of the nervous organic alterations in the first period of life, we are compelled to weigh carefully the least change in nervous reactions, especially those reflexes which are usually tested. The differences, sometimes very marked, that one encounters among the results reported by various authors who have studied the reflexes in the new-born are due, I think, to some fault in the methods of observation and the interpretation.

Examination of the reflexes in the child, and much more in the new-born infant, presents great technical difficulty, which must be overcome with much patience and requires numerous and careful observations. The physiologic muscular hypertonia of the new-born; the incessant moving about, and the difficulty in limiting the intensity and extension of a stimulus hinder both production of the reflexes and their interpretation, besides causing marked variability in reactions under the same conditions. Therefore, it is easy to note, in several successive tests of a reflex, variations in the result, which compel one to repeat the test several times, in order to reach precise definite conclusions.

Besides, one must bear in mind that after the same reflex has been tested repeatedly in the new-born, a kind of muscular fatigue or an

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adaptation to the stimulus results, so that, in protracting the observation, one, at last, excites a reflex which is entirely different from the first ones in quality and intensity.

Another factor in the variation in the reflex is the means employed for stimulation. Intense and brief stimulation, with rough stinging objects can produce a reaction quite different from that obtained by gentle stimulation with smooth objects. A vigorous stimulation elicits not only the reflex which is sought, but also a series of muscular contractions which are extraneous to those peculiar to the reflex and which interfere with its interpretation.

These various conditions make research difficult, and largely explain the differences in results obtained by observers.

My researches were made on eighty-eight new-born infants in the first week of life, and have been carried out, for the most part, during the first two days after birth.

The examinations have been made repeatedly under varying conditions; with the baby sleeping, waking, weeping, resting, etc.; never tiring the baby, and examining one or two reflexes at a time. The final conclusions as to the behavior of each reflex are the synthesis of various examinations carried out under different circumstances.

All new-born infants observed were constitutionally sound and had no disease. In analyzing the results, I have considered the various etiologic factors: age, sex, weight, etc., but as I have noted no relation between them and the behavior of the reflexes, consideration of each factor singly is not worth while. It may be noted, in a general way, that an inverse relation exists between the tendinous and cutaneous reflexes according to body weight; that is, the greater the weight and development of the baby, the more vigorous the cutaneous reflexes and the weaker the tendinous reflexes, and vice versa. This observation, however, has some exceptions.

A CONSIDERATION OF THE VARIOUS REFLEXES

In presenting the results obtained, it seems necessary to consider each reflex separately.

Cutâneous Reflexes.—The first and most important is the plantar reflex. Babinski,[1] on attributing the phenomenon he described to alterations of the pyramidal tract, deduced, as a corollary of this conception, that the phenomenon should be physiologic in the new-born, because of the insufficient myelinization of that tract at birth. In fact, his own researches and those of others later confirmed this deduction experimentally.

1. Babinski: Semaine méd., 1898.

But latterly some observers (Gindiceandrea,[2] Finizio[3]) have noted that by stimulating the sole of the new-born, one produces flexion, as occurs normally in the adult, instead of extension of the toes. Therefore, while some observers think that, in healthy new-born children in the first week, the plantar reflex consists in the dorsal flexion of the toes, others believe that plantar flexion is the rule. Engster,[4] in 232 new-born children, found dorsal flexion constantly, except in two cases in which there was plantar flexion, and in eight in which the reflex was not elicited. Léri,[5] in 166 new-born infants, found, as a rule, the dorsal flexion and, exceptionally, the plantar.

On the contrary, Finizio,[3] in fifty new-born infants, found that the plantar reflex was absent in 5 per cent., was undecided in 10 per cent., and consisted in extension in 15 per cent., and in flexion in 70 per cent.

The results of my examinations led me to a conclusion analogous to Feldman's;[6] that is, the usual response of the plantar reflex is the plantar flexion of the toes. For reflex stimulation, I employed the dorsal surface of the little finger nail, passed swiftly, thinking such a stimulus the best on account of its uniformity. In the reflex interpretation, many times, the classification of the type was not easy, because the toe movement was very undecided because of the alternation of flexion and extension in response to successive stimuli.

When one stimulates the sole, the first responsive movement generally accentuates the position of the toes at the instant of stimulation. This position, normally, consists in extension of the great toe and flexion of the other toes, but at times the four toes extend and the great toe is flexed, or all toes extend or are flexed together.

These movements are not constant, but extremely variable, so that, several times successively, each response may contradict the one preceding.

In seeking the normal reflex for a given new-born, I have not considered the first seventy elicited, but the type proved most frequent. I thus noted that there is but little difference between the percentage of reflexes showing flexion and those showing extension, having found the former in 57 per cent. and the latter in 43 per cent. On no occasion was there complete failure of the reflex; on the contrary, reflexes in the new-born are very pronounced.

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2. Gindiceandrea: Soc. Lancisiana d. osp. di Roma, 1899.
3. Finizio: La Pediatria, August, 1900.
4. Engster: Wien. klin. Wchnschr. **18**:567, 1905.
5. Léri, M. A.: Gaz. d. mal. inf. **5**:277, 1903.
6. Feldman, W. M.: Nature of Plantar Reflex in Early Life and Causes of Its Variation. Am. J. Dis. Child. **23**:406 (Jan.) 1922.

Response to the plantar stimulation is given not only by toe movements, but by flexion movements of the whole foot; and the stronger the stimulation, the more intense the response. These movements, the result of special reflexes, have no clinical value in the new-born.

The plantar reflex, always present, is much attenuated in premature infants and in new-born infants who are under weight.

Abdominal Reflex.—This is elicited with difficulty, and must be tested during sleep or while the baby is nursing, is hardly perceptible in 77 per cent., rather intense in 16 per cent., and absent in 7 per cent. It is seldom elicited in well-developed and well-nourished new-born infants.

Cremasteric Reflex.—This by some authors (Griffith)[7] has been constantly found at birth; by others (Finizio[3]), it is noted only exceptionally in the new-born (2 per cent.). I found it present in 92 per cent., the intensity varying with the descent of the testicles.

Corneal and Pharyngeal Reflexes.—These reflexes are present in all new-born infants and are very vigorous.

Tendinous Reflexes,—In order to provoke these reflexes, I employed percussion with a small hammer. I tested various reflexes, but the doubtful results I obtained led me to consider only the knee reflex, because it is difficult to differentiate the movements due to tendon contraction from that caused by the hammer. I have divided the knee reflex into three types according to liveliness, and I found that it is normal in 20.4 per cent.; exaggerated in 54.5 per cent.; much exaggerated in 21.6 per cent., and absent in 3.5 per cent. I have further noted a difference of intensity in the two reflexes (16 per cent.), and even the presence of the reflex in one knee and the absence in the other (5.6 per cent.). This condition is commonly found in premature infants.

Pupillary Reflexes.—There is great difficulty in classifying these reflexes, because of their variety. I found in 17 per cent. obstinately myotic pupils, with barely perceptible oscillation toward the light. In 20.5 per cent., there were enlarged pupils, with slow movements. The reflex as it occurs in 62.5 per cent. is a series of alternations which begin with a contraction provoked by a luminous stimulus, followed by dilatation. Thus there develops a movement of pendulum type which gradually slackens, then recommences at a new stimulus, or sometimes without it. Several times the dilatation of the pupils was not in relation to the quantity of light reaching the eye, nor were the movements in relation to the variations of light.

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7. Griffith, J. P. C.: The Diseases of Infants and Children, Philadelphia, W. B. Saunders Company **1**:65, 1919.

From these results, one can deduce that the physiologic significance of reflexes in the new-born varies greatly from that of reflexes in the adult. The first difference consists in their greater liveliness, a result of lack of development of the nervous system and cerebral inhibition, not on physiologic hypertonicity. This activity is observed only in the first tests of the tendinous reflexes, diminishing if repeated stimulation causes the muscular fatigue. For cutaneous reflexes, the initial activity does not change.

More remarkable are differences in mode of response, especially for plantar and pupillary reflexes, so that while they have great diagnostic value in the adult, they have none in the new-born.

The variableness is more evident in the cutaneous and pupillary than in the tendinous reflexes, which behave very much as in the adult. As to the presence or absence of reflexes, one can say that they present no variations from those of the adult. With patience, waiting for a right moment, one may succeed in eliciting all reflexes in the new-born. From my observation, I have concluded that almost all reflexes are present at birth, and only exceptionally some one of them does not appear until sometime during the first months. This is in opposition to the observations of Bychowsky,[8] who says that many reflexes make their appearance during the first months of life.

CONCLUSION

The great variability of reflexes in the new-born, whose modification and intensity vary widely, makes it impossible to attach to them the pathognomonic importance they have in the adult.

It is difficult, unless there are great deviations, to judge whether the intensity of a given reflex is strengthened or weakened, if it reveals pathologic nervous alterations, when even in normal conditions such remarkable differences exist. It may be that besides modification and intensity, the presence or absence of reflexes, in the new-born, may have pathognomonic importance. Since all reflexes, cutaneous and tendinous, are present at birth, the absence of one or more of them only can give some indication of nervous injury.

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8. Bychowsky: Ztschr. f. Nervenh. **34,** January, 1923.

EXOPHTHALMIC GOITER IN CHILDHOOD WITH SOME UNUSUAL MANIFESTATIONS*

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During the past few years, unusual interest has been aroused in the study of thyroid conditions. Perhaps the most important stimulus has been the more general application of basal metabolism determinations. The improved operative technic and the more extensive use of roentgen-ray therapy have also played an important rôle.

The occurrence of three cases of exophthalmic goiter in children in private practice suggested a study of this condition as manifested in childhood. Two of these cases were observed also on the pediatric service at Mount Sinai Hospital.

Exophthalmic goiter was known many centuries ago. The ancient Romans realized that slaves afflicted with this condition were unfit for strenuous work. It was not recognized, however, that exophthalmos was a symptom of a disease until Flajani's work in 1780. Perry, in 1786, noted the same fact. The description of the disease as we know it was given by Graves in 1835 and by von Basedow in 1843. The first case in a child was recorded by Henoch-Romberg [1] in 1851.

INCIDENCE, AGE AND SEX

Although exophthalmic goiter is rare in childhood, in the course of years a large number of cases have been reported. In a series of 1,512 cases at the Mayo Clinic, there were five children under 10 years of age (0.3 per cent.). Klein [2] mentions a series of 3,477 cases, which included 184 in children under 15 years (5 per cent.). Barret,[3] who made a most exhaustive study of the condition in childhood, believes the ratio of children to adults is 1:50. He collected thirty-nine cases in children reported in the literature before 1901. The youngest was 2½ years. There were three cases in children less than 5 years of age; eleven between 5 and 10 years, and twenty-five from 10 to 15 years. The youngest patient in the Mayo Clinic series was 4 years. A case cited by Ochsner and Thompson [4] may have been congenital. A woman of 35 years developed exophthalmic goiter during pregnancy. A premature birth occurred at seven and one half months. Five weeks after birth, the infant's eyes became abnormally prominent. No men-

* Received for publication, July 19, 1923.
* Read before the American Pediatric Society at the thirty-fifth annual meeting, May 31, June 1 and 2, 1923, at French Lick, Ind.

1. Henoch-Romberg: Klin. Wahrnehm and Beobacth., Berlin, 1851, p. 178.
2. Klein, S.: Arch. Pediat. **39**:786 (Dec.) 1922.
3. Barret, G.: Paris Theses, 1901.
4. Ochsner and Thompson: The Surgery and Pathology of the Thyroid and Parathyroid Glands, p. 192, 1910.

tion was made, however, of the thyroid or the pulse rate in the original report by Schmauch. During the first year of life, the condition is extremely rare. The ages of our patients when symptoms of the disease first became manifest were 4, 5, and 7 years, respectively.

Sex distribution shows a definite preponderance of females. In Barret's review of thirty-nine cases in children, there were twenty-eight girls and eleven boys. In the series of cases mentioned by Klein, 84 per cent. of the cases were in girls. All three cases of our group are in girls.

ETIOLOGY

The etiology of exophthalmic goiter has been the subject of considerable experimentation, speculation and dispute. One group of workers, Filelines, Walburton and Tedeschi, thought the disease had a bulbar origin. They sectioned the restiform bodies and produced the symptoms of hyperthyroidism in animals. Trousseau, Charcot, Gerhardt and Sattler believed the condition was a neurosis of the whole vegetative nervous system. Nutkine and Blum thought there was a thyroid insufficiency and a consequent insufficient detoxication of the body. Basedow believed the condition due to a poisoning of the blood by thyroid products. Hart and Bircher suggested a thymic origin.

Moebius believed the disease was produced by a hypersecretion of the thyroid gland. This opinion has been widely held for a long time. The recent studies of exophthalmic goiter by Kessel, Lieb and Hyman,[5] however, seem to refute this view. They point out that this condition may exist in the presence of a normal or colloid thyroid and that hyperplasia of the gland may coexist with myxedema. In no instance has it been possible to develop artificially, by the administration of large doses of thyroid extract to man or animal, a typical case. They believe the condition to be "(1) a clinical collection of sympathomimetic symptoms (tachycardia, exophthalmos, sweating, asthenia, polyrrhea, etc.) associated with (2) metabolic upset (elevated basal metabolism) and usually accompanied by (3) hyperplasia of the thyroid gland." The sympathomimetic symptoms may be developed by stimulation of the thoracicolumbar division of the involuntary nervous system. The ultimate cause of the disease, then, must act primarily or secondarily through the involuntary nervous system.

HEREDITY

Heredity has played an important rôle in a large number of reported cases. Dejerine[6] believed that exophthalmic goiter occurs in neuro-

5. Kessel, Leo; Lieb, C. C., and Hyman, H. T.: Exophthalmic Goiter and Involuntary Nervous System, J. A. M. A. **79**:1099 (Sept. 30) 1922; **79**:1213 (Oct. 7) 1922.

6. Dejerine: Thesè d'argrey, p. 157, 1886.

pathic families. Dubrenil-Chambardel [7] reported a family in which the grandmother, mother and two daughters of 4 and 7 years, all had exophthalmic goiter. Lonques and Lermoyez [8] described a family with seven cases of exophthalmic goiter. Climenko recorded the history of a family in which the mother, two daughters and two grandchildren, girls of 6 and 10 years, all had the disease. In a report by Frantz,[9] a girl of 9 years and her mother were afflicted with the condition. In our group of three cases, careful inquiry into the family histories did not reveal any hereditary tendencies.

SYPHILIS

Syphilis was thought to be the underlying factor in several cases. Gauches and Salin [10] record a case in which hereditary syphilis manifested itself in the form of polyglandular hyperthyroidism. Hazen [11] cites the case of a girl with secondary syphilis who developed enlargement of the thyroid with symptoms of hyperthyroidism. Rost [12] reported a case of exophthalmic goiter in a girl of 12 years with marked toxic symptoms, whose blood Wassermann reaction was four plus. She showed definite improvement under antisyphilitic treatment. In none of our cases was there any history of syphilis. The Wassermann test was negative in two of the cases. In one, it was not made.

PATHOLOGY

The structure of the thyroid gland and its pathology has been clearly described by Marine.[13] Uniform enlargement of the thyroid may be produced by a hyperplastic or a colloid gland. In the former, the epithelium is higher and the walls of the alveoli may be thrown up into plications. There is increased blood vessel supply and at times round-cell infiltration of the stroma. The colloid is diminished.

In the colloid gland, there is a formation of large amounts of colloid material which stretch the alveolar spaces and produce a flattened epithelium. There is marked thickening of the walls of the blood vessels. Transitional forms are found in which there may be colloid, in a hyperplastic gland; and vice versa. Discrete enlargements of the gland may be produced by adenomas or cysts. An adenoma may have the same structure as normal, colloid or hyperplastic thyroid tissue.

Thyroxin, an iodin-containing substance, has been isolated by Kendall,[14] as the specific secretion of the thyroid gland.

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7. Dubrenil-Chambardel: Province Med., p. 262, 1907.
8. Lonques and Lermoyez: Rev. Neurol. **35**:20 (Jan.) 1919.
9. Frantz, M. H.: New York M. J. **113**:275 (Feb. 12) 1921.
10. Gauches and Salin: Bull. Soc. franç. de dermat. et syph. **23**:62, 1912.
11. Hazen, H. H.: Am. J. Syphilis **3**:205 (April) 1919.
12. Rost, William: Arch. Pediat. **39**:458 (July) 1922.
13. Marine, David: J. Lab. & Clin. Med. **3**:40 (Oct.) 1917.
14. Kendall, E. C.: J. Biol. Chem. **40**:265 (Dec.) 1919.

One of our patients, the child of 5 years, was operated on by Dr. Crile, and portions of the right and left lobes of the thyroid were removed. There was considerable colloid present, with slight hyperplasia of the parenchyma. No tumors were found.

SYMPTOMATOLOGY

The cardial symptoms of exophthalmic goiter are tachycardia, exophthalmos and enlarged thyroid gland. The most important diagnostic test is an increased basal metabolism. Barret, from his study of thirty-nine cases in childhood, believes that tachycardia is the first important symptom to develop. The average pulse rate ranged between 100 and 120. In six cases, the rate was 150 or over. In our cases, the pulse rate was in direct relation to the severity of the condition, the mildest case having the lowest rate. In the three cases, the range of the pulse rates before treatment was: first case, from 100 to 110; second case, from 120 to 130; third case, from 160 to 180.

The exophthalmos is usually less marked in children than in adults, but its presence is generally definitely observed. In Barret's report, it was absent in only eight of the thirty-nine cases. In our experience, it was distinctly present in all three cases, and the degree of exophthalmos was in direct relation to the severity of the condition, the case of the most rapid pulse rate and the highest basal metabolism having the most marked prominence of the eyes. Graefe's and Stellwag's signs were present in all our cases. Moebius' sign was elicited in one of the three cases.

Enlargement of the thyroid gland was noted in all our cases. A distinct bruit over the gland was heard in two instances.

The basal metabolism test has proved to be the most important guide in diagnosis as well as in the determination of the severity of the disease. In 182 cases of exophthalmic goiter in adults, before any treatment, Sandiford [15] found an average metabolic rate of + 51 per cent. In children afflicted with a disease manifested by considerable excitability, it is often difficult to perform the test, as complete muscular relaxation is essential. We were fortunate in obtaining the perfect cooperation of our patients. The tests were made by Dr. Herman Lande of Mount Sinai Hospital. The Tissot method of indirect calorimetry was employed. Benedict and Talbot's standards, based on weight, were used. The results in the three cases before treatment were: fiirst case, + 12 per cent.; second case, + 20 per cent.; third case, + 52 per cent. Clinically, the degree of severity of the symptoms and signs corresponded with the degree of elevation of the metabolic rate.

15. Sandiford, Irene: Endocrinology **4**, No. 1.

The minor symptoms of exophthalmic goiter are tremor, excitability, polyphagia, diarrhea and hyperhidrosis. Osler [16] believed tremor to be one of the cardinal symptoms, but in childhood it has not been frequently observed. It was noted in only four of Barret's series of thirty-nine reported cases. In a number of later reports, its absence was noted. In two of our cases, a fine tremor of the hands was observed. Hyperhidrosis was present in all three cases.

Alertness and irritability were present in all our cases. The mentality of the children was above the average. In the three cases, the height of our patients was noticeably above normal, in one case 2 inches (5 cm.), in the other cases, about 4 inches (10 cm.). The weight in two cases was normal; in one case, with the markedly elevated basal metabolism, 5 pounds (2.27 kg.) below normal. In the latter, too, constant marked hunger and diarrhea were annoying symptoms of the disease.

An unusual manifestation was the development of severe recurrent attacks of ketosis in this case. Major [17] has recently called attention to this condition following roentgen-ray treatment of the thyroid and partial thyroidectomy. Crile [18] believes that in fatal cases of exophthalmic goiter the usual cause of death is acidosis, and that so-called postoperative hyperthyroidism is mainly acute acidosis. We have not found any records of this complication, however, in cases before treatment was instituted. The first time we had the opportunity of seeing our case was during such an attack.

We found the child of 4 years in deep coma. The room was filled with the fruity odor of the ketone bodies. The respiration rate was 60 per minute; the pulse rate, 180; the temperature, 103 F. There was no cyanosis. There were marked convulsive twitchings of all the extremities. The child could not be aroused. She seemed to be in extremis. The urine showed much acetone and diacetic acid. We immediately gave a hypodermoclysis of 250 c.c. of 5 per cent. glucose solution, repeating it in half an hour. Within an hour, the improvement was remarkable. The patient became perfectly conscious, the respirations and pulse rate diminished considerably and she was able to take fluids by mouth. Her condition was normal in twenty-four hours.

It was after this attack that the symptoms and signs of exophthalmic goiter became evident. The patient has had three similar attacks since then, several months apart, each time responding perfectly to the administration of glucose solution by hypodermoclysis. We are now giving her glucose in her diet regularly, as we do in every severe case of acidosis, from 1 to 2 drams (3.75 to 7.5 cm.) a day, and during the past six months she has had no attacks. The exophthalmic goiter, however, has grown progressively worse. The mother has refused operative interference. During one of the attacks of ketosis, the child was in the hospital and a complete blood examination was made. There were no abnormal findings except the diminution of the carbon dioxid content, which was 34.7 per cent. by volume. The blood sugar was 0.15 per cent.

16. Osler, William: Principles and Practice of Medicine, p. 878, 1912.

17. Major, R. H.: Acidosis in Hyperthyroidism, J. A. M. A. **80**:83 (Jan. 13) 1923.

18. Crile, G. W.: Ann. Surg., Sept. 25, 1915.

Blood counts were made in all our cases, but did not show the lymphocytosis frequently found.

TREATMENT

The treatment of exophthalmic goiter has passed through a number of stages. Jacobi,[19] who reported four cases in children between the ages of 9 and 13 years in 1879, employed arsenious acid, atropin and extract of ergot as the most successful drugs. A number of other reports included the use of digitalis, iron and salicylate of soda. Electricity was employed in some of the earlier cases. Thyroid and thymus extracts were used.

With the advent of modern surgery great strides were made in the management of thyroid conditions. The preoperative care, the operative technic and the postoperative vigilance have been perfected to a remarkable degree. A report from the Mayo Clinic showed that in 1,093 operations for exophthalmic goiter there were eleven deaths, or 1.005 per cent. Of these, 523 were partial thyroidectomies, with a mortality of 0.96 per cent.

Sandiford has demonstrated the fall in the basal metabolic rate after operation in cases of exophthalmic goiter.

The roentgen ray has been employed, with some very favorable results. The most recent work along this line, by Means and Holmes,[20] showed that in forty-four recent cases of exophthalmic goiter treated by roentgen ray twenty-eight patients were improved. Of these, twelve were apparently cured and sixteen improved but not entirely well. In no instance was a case made worse. In the favorable cases, there was a rapid fall in pulse rate (from an average of 115 to 89) and basal metabolism (from an average of 55 per cent. to + 21 per cent.

Radium emanations have been used by Terry in the treatment of exophthalmic goiter, mainly in preparation for thyroidectomy. Of sixteen patients, two were cured by radium alone; ten were well after resection of the thyroid, and four died after operation.

As so many good results were reported from various therapeutic procedures, Kessel, Lieb and Lande,[21] in their recent studies of this condition, were prompted to determine whether exophthalmic goiter did not show a tendency to spontaneous recovery. They studied the natural course of the disease in fifty cases under hygienic conditions and the least possible psychic disturbance. No specific treatment was

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19. Jacobi, A.: New York M. Rec., July 5, 1879.

20. Means, J. H., and Holmes, G. W.: Further Observations on the Roentgen-Ray Treatment of Toxic Goiter, Arch. Int. Med. **31**:303 (March) 1923.

21. Kessel, Leo; Hyman, H. T., and Lande, Herman: A Study of Fifty Consecutive Cases of Exophthalmic Goiter, Arch. Int. Med. **31**:433 (March) 1923.

employed. Bed rest was given from six to ten weeks. They state that the tendency to recovery in these patients was "astounding." Forty-one, or 82 per cent., of the patients were "socially or economically restored." There was a marked decrease in the basal metabolic rate. An absolute restoration to a perfectly normal condition, as far as their observations up to the time of writing went, rarely occurred.

In our group of three children, one with a case of moderate severity, with a basal metabolism of + 20 per cent. and a pulse rate of 120, was operated on by Dr. Crile about three months ago. A partial thyroidectomy was performed. She was seen by us recently, and the marked improvement in her condition was evident. Her mother reported considerable improvement in nervousness and irritability. The eyes were much less prominent, though a slight exophthalmos persisted. The pulse rate had decreased to 102. No tremor was elicited. A nocturnal enuresis which she had previously had disappeared. The basal metabolism was normal.

A second case of moderate severity has been observed at intervals for the past two years. As far as we know, no specific treatment has been employed. The patient has had occasional periods of bed rest, but has attended school most of the time. Her basal metabolism has remained about the same, + 16 per cent. The pulse rate varies between 110 and 120.

In the most toxic case of the group, with a basal metabolism of + 52 per cent. and pulse rate ranging between 160 and 180, the patient has had a long period of rest treatment. She has been in bed at intervals for periods from two to four weeks. Her condition has not improved. The exophthalmos is more marked. The pulse rate ranges between 150 and 160. The thyroid gland has increased in size. The attacks of ketosis, however, have not recurred recently. The mother has refused consent for operation. Roentgen-ray treatment is under consideration.

In the light of all the recent evidence regarding treatment, it seems the most rational procedure to institute first a regimen of strict physical and psychical rest for six to ten weeks. If the patient shows no improvement, a short period of roentgen-ray therapy should be tried. Thyroidectomy should be performed if there is no response to the roentgen ray. On account of the toxic action on the heart in the severe cases, it is safer not to wait too long before operation.

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EXPERIMENTAL OBSERVATIONS ON THE ETIOLOGY OF CHOREA*

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Numerous investigators have made cultures of the throat, tonsils, blood and spinal fluid of patients with chorea. Collins [1] isolated from the blood of a patient with severe chorea gram-positive cocci which grew in pairs, or in chains of from four to six. La Fetra [2] reported the finding of *Streptococcus viridans* in the blood of two patients with chorea. Camisa [3] isolated a diplostreptococcus from the blood of six of nine patients with chorea minor. The blood of twenty-one patients was cultured by Quigley,[4] and in nine of these he found small cocci arranged in pairs and in short chains. Positive results on culturing the spinal fluid were obtained in thirteen of twenty-one cases, and the organisms in eight of the thirteen resembled those found in the blood. Poynton and Paine [5] obtained a diplococcus from the spinal fluid of two patients dying with rheumatic fever associated with symptoms of chorea. With one of these strains, arthritis, endocarditis and pericarditis were produced in rabbits. These authors were able to demonstrate microscopically the diplococci around the pial vessels in the two fatal cases. From the blood, brain, tissues and heart valves from a fatal case of chorea following arthritis, Westphal, Wassermann and Malkoff [6] obtained a streptococcus with which arthritis could be produced in rabbits. Richards [7] obtained *Streptococcus viridans* from the blood in fourteen of 104 cases of arthritis, and he was able to demonstrate the presence of the same organism in four of fifty-four joint cultures. The same organism was found in cultures of the blood in five of sixteen cases of chorea, and it was also demonstrated in cultures from the

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1. Collins, J. R.: Rheumatism and Chorea, Brit. M. J. **1**:220-221, 1913.

2. La Fetra, L. E., discussion of Strauss, I.: Present Conception of Chorea, Arch. Pediat. **32**:135-136, 1915.

3. Camisa, G.: Bakteriologische Untersuchung des Blutes der Chorea minor Kranken, Centralbl. f. Bakteriol. **57**:99-107, 1910-1911.

4. Quigley, W. J.: Observation on the Bacteriology of Chorea, J. Infect. Dis. **22**:198-204 (March) 1918.

5. Poynton, F. J., and Paine, A.: Some Investigations on the Nervous Manifestations of Acute Rheumatism, Lancet **2**:1760-1765, 1905.

6. Westphal, Wassermann and Malkoff: Ueber den infectiösen Charakter und den Zusammenhang von acutem Gelenkrheumatismus und Chorea, Berl. klin. Wchnschr. **34**:638-640, 1899.

7. Richards, J. H.: Bacteriologic Studies in Chronic Arthritis and Chorea, J. Bacteriol. **5**:511-525 (Sept.) 1920.

tonsils, teeth and nasal mucous membrane. The spinal fluid in nineteen cases of chorea was found sterile by Morse and Floyd,[8] but positive results were obtained in five of twenty-six cases in which cultures of the blood were made. Streptococci were demonstrated in three of the five positive cases. Dick and Rothstein[9] have reported the occurrence of choreic symptoms in a dog following the intravenous injection of a streptococcus cultured from the throat of a patient with chorea of five years' duration. Floyd[10] isolated streptococci from teeth and tonsillar crypts in seventeen of twenty cases of chorea, and was able to produce endocarditis and swelling of the joints in rabbits with these strains. The cultures of the blood in all cases were negative.

The findings at necropsy in a patient with chorea, who had had numerous attacks of rheumatism, are reported by Dana.[11] There was chronic leptomeningitis of a convexity of the brain, slight meningitis of the upper spinal cord and slight meningo-encephalitis. Microscopic examination of tissues of the superior parietal lobules revealed thickening of the pia, the result of connective tissue proliferation, without exudate or round-cell infiltration. Gram-positive diplococci were found, free and on the inner surface of the membrane, in sections stained by Weigert's method.

These bacteriologic studies, while indicating that chorea is a streptococcic disease, do not furnish convincing proof that this is so, because in only a few instances has the disease been produced experimentally with the organisms isolated. My own studies in this field have yielded results which furnish important additional proof that chorea minor is the result of a particular streptococcic infection.

EARLY OBSERVATIONS ON INTRAVENOUS INJECTION

The hypothesis that chorea might be due to a streptococcus having peculiar neurotropic properties took definite form in March, 1910, when chorea developed in a dog and a rabbit, after I had injected intravenously a streptococcus isolated from the blood during life in a fatal case of typical chorea. A low grade meningitis, most marked around the vessels in the cerebral cortex, and subcortical hemorrhages were found in both animals. The streptococcus in pure culture was recovered from the slightly turbid cerebrospinal fluid. The rabbit also

8. Morse, J. L., and Floyd, Cleveland: A Study of the Etiology of Chorea, Am. J. Dis. Child. **12**:61-72 (July) 1916.

9. Dick, G. F., and Rothstein, T.: A Streptococcus Producing Symptoms of Chorea in a Dog, J. A. M. A. **61**:1376 (Oct. 11) 1913.

10. Floyd, Cleveland: A Study of Streptococci Obtained from the Mouth in Cases of Chorea, J. M. Res. **41**:467-479 (May) 1920.

11. Dana, C. L.: On the Microbic Origin of Chorea: Report of a Case, with Autopsy, Am. J. M. Sc. **107**:3-38, 1894.

had lesions of the joints, the fascial sheaths of muscles and the heart valves. Similar results were obtained on four widely separated occasions, following intravenous injection of a series of animals with cultures from tonsils during the acute stage of this disease.

Five rabbits and two white rats of a total of thirty-five animals injected intravenously with the streptococcus isolated from the joint fluid, blood or infection-atria of patients with acute rheumatic fever developed chorea-like symptoms, besides lesions of the joints, muscles and heart.[12] The postmortem findings in the central nervous system consisted of small circumscribed meningeal hemorrhages and slightly turbid cerebrospinal fluid in the experiments of short duration; and of localized grayish nodular thickening of the pia and, microscopically, of subcortical areas of round-cell infiltration in experiments of longer duration.

Muscular movements resembling those in chorea developed occasionally following intravenous injection of cultures of streptococci from various other diseases. Choreiform movements occurred in five of a large number of animals following the injection of mass cultures from the tonsils or infected teeth of patients with chronic myositis, with or without arthritis;[13] three times with cultures of tonsils which were removed on account of their large size and because of repeated attacks of tonsillitis in persons that were well; and in one instance each following the injection of a large number of animals with mass cultures from tonsils of patients with appendicitis, ulcer of the stomach, cholecystitis, parotitis, herpes zoster and goiter. In these animals, the lesions of the central nervous system consisted of low grade meningitis and meningeal and subcortical hemorrhages (Fig. 1) in the experiments of short duration, and of perivascular and localized infiltration by round cells in the pia, and subcortical areas of necrosis and cellular infiltration (Fig. 2) in the experiments of longer duration. In the latter group of animals, the lesions of the central nervous system were believed to be more or less accidental because embolic lesions, chiefly in the organs corresponding to those affected in the patient from whom the cultures were obtained, were also found. The lesions were always due to streptococci, notwithstanding the fact that the cultures injected usually also contained a variable number of other bacteria. The streptococci isolated from the lesions or from the spinal fluid produced a greenish

12. Rosenow, E. C.: The Etiology of Acute Rheumatism, Articular and Muscular, J. Infect. Dis. **14**:61-80, 1914.

13. Rosenow, E. C., and Ashby, Winifred: Focal Infection and Elective Localization in the Etiology of Myositis, Arch. Int. Med. **28**:274-311 (Sept.) 1921.

zone around the colonies on blood-agar plates. This was true alike in the cases of chorea, rheumatic fever and myositis, as well as in the other diseases.

The experimental results in chorea parallel the clinical observations as regards the common occurrence of lesions in joints, muscles and endocardium in cases of chorea. The experimental results in rheumatic fever and myositis support the supposed etiologic relationship between chorea and rheumatic affections, and the rare occurrence of chorea-like symptoms in the animals injected with strains from other diseases may be regarded as representing the chorea in man which sometimes develops in the course of acute pyemia and other infections.

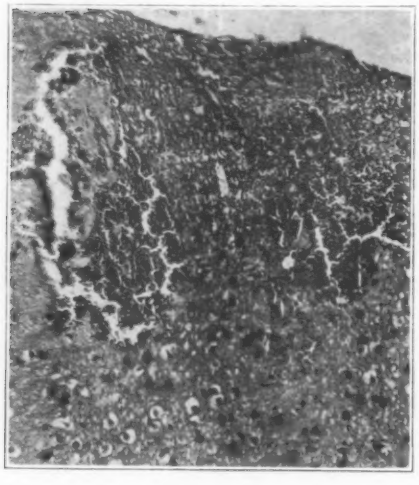

Figure 1

Figure 2

Fig. 1.—Localized subcortical hemorrhages in rabbit that developed choreiform movements forty-eight hours after an intravenous injection of a streptococcus from the tonsil in a case of subacute arthritis and myositis; hematoxylin and eosin; × 100.

Fig. 2.—Area of necrosis and infiltration in the subcortical region in the lower rolandic region of a rabbit that developed marked incoordinate movements of the head four days after an intravenous injection of a streptococcus from the parotid duct in a case of epidemic parotitis; hematoxylin and eosin; × 75.

With these observations in mind, I thought it worth while to study additional cases of chorea by the methods developed in connection with studies on encephalitis and allied conditions, and to compare the localizing and symptom-producing power and other properties of the streptococcus suspected of having etiologic relationship in chorea with strains of streptococci from cases of encephalitis with which various forms of encephalitis have been produced in animals.

RECENT EXPERIMENTS ON INTRACEREBRAL INOCULATION

In the experiments on encephalitis [14] and epidemic hiccup,[15] it was found that, while symptoms and lesions of the central nervous system developed in some instances following intravenous injection, intracerebral inoculation was necessary in order to measure accurately the infecting power of the bacteria suspected of having etiologic significance. Through the coöperation of Dr. Helmholz, of the Section on Pediatrics, cultures from four cases of typical chorea were obtained and observations were made following injections in animals by the intracerebral method.

REPORT OF CASES

Case 1.—A girl, aged 13 years, suffered from rheumatic pains, and swelling of the arms and legs following an attack of tonsillitis. This continued for about one month, when an attack of typical chorea developed. Animals were inoculated with cultures from this patient three months after the onset of symptoms.

Case 2.—A girl, aged 6 years, developed incoordinate movements of the mouth and the limbs several days after the extraction of a tooth. Animals were inoculated with cultures from this patient one month after the onset of symptoms. The tonsils had been removed eight days before. The incoordinate movements were severe, and examination revealed a moderate infection of the nasopharynx, many carious teeth and mitral endocarditis.

Case 3.—A girl, aged 8 years, developed incoordinate movements of the extremities from no apparent cause. The tonsils were large, and the crypts were filled with cheesy material from which pus could be expressed. The tonsils were removed five weeks later, and the patient ultimately recovered completely. About two weeks after the development of the incoordinate movements, animals were inoculated with cultures from this patient.

Case 4.—A girl, aged 12 years, developed a mild attack of chorea about ten days before our study. The characteristic organism was isolated from pus expressed from the tonsils, and from the nasopharynx. The tonsils were found to be infected, and were removed two weeks later. Several small abscesses were found, from which the streptococcus was again isolated. With rest in bed for three months, the patient completely recovered without developing demonstrable cardiac lesions.

The material cultured and injected was pus expressed from the tonsils, and the exudate from the nasopharynx obtained with wire swabs bent to the proper angle. Suspensions of each were made in 2 c.c. of sodium chlorid solution. This suspension was used for the direct injection of animals and to inoculate blood-agar plates and tall tubes of glucose-brain broth. Two rabbits were injected routinely with the suspensions, one receiving 0.1 c.c., the other 0.2 c.c. If no symp-

14. Rosenow, E. C.: Experimental Studies on the Etiology of Encephalitis: Report of Findings in One Case, J. A. M. A. **79**:443-448 (Aug. 5) 1922.

15. Rosenow, E. C.: The Production of Spasms of the Diaphragm in Animals with a Streptococcus from Cases of Epidemic Hiccup, J. Infect. Dis. **32**:41-71 (Jan.) 1923; The Production of Spasms of the Diaphragm in Animals by Living Cultures, Filtrates, and the Dead Streptococcus from Cases of Epidemic Hiccup, J. Infect. Dis. **32**:72-94 (Jan.) 1923.

toms developed within twenty-four hours, other rabbits were injected with the primary culture in glucose-brain broth. If suggestive symptoms developed, the strains isolated from the central nervous system of the animals injected directly with the suspension were used for subsequent injections. The dose ranged from 0.1 c.c. of a 1:1,000 dilution to 0.2 c.c. of the undiluted glucose-brain broth culture. The number of animals injected depended largely on the results obtained. In order to rule out the possibility of a slowly growing virus, pure cultures of the streptococcus obtained from animals showing characteristic symptoms were injected after many rapidly made subcultures.

RESULTS

Seven rabbits were injected intracerebrally with cultures from Case 1, three rabbits from Case 2, two from Case 3 and nineteen rabbits and one dog from Case 4. Positive results were obtained following injections of cultures from Cases 1, 2 and 4. The two rabbits injected intracerebrally with the salt solution suspension of the culture from Case 3 remained well. Of the total of thirty-two animals injected, twenty-two (69 per cent.) developed varying degrees of ataxia; in eight (25 per cent.), the movements were definitely choreiform in type; only three developed unusual weakness of extremities; two developed marked tremor; two, markedly increased respiration, and ten, clonic contractions of the muscles of the extremities or of the neck. Only two of the twelve rabbits injected in the first animal passage developed spasms of the muscles; whereas, eight of the remaining nineteen that were injected with the streptococcus in the second animal passage developed this symptom. The ataxia or incoordinated movements were often extremely marked and the animals frequently lost their balance when made to hop. All movements disappeared during sleep. Lethargy was not observed in any of the rabbits injected with the chorea strains. In nine rabbits, no symptoms were observed. Three of these were injected directly with suspensions of nasopharyngeal swabs in sodium chlorid solution and were observed for eleven, thirty and fifty-eight days, respectively. Of the remaining six, one died in forty-eight hours, the others during the night following injection. All of the six received inoculations of the streptococcus in the second animal passage. The findings at necropsy consisted, in the main, of congestion of the vessels of the meninges and moderate or slight turbidity of the cerebrospinal fluid. Occasionally, localized hemorrhages in the pia, especially over the cerebral cortex and cerebellum, were found.

Cultures were made from the brain and the blood of twenty-seven animals. The green-producing streptococcus was isolated from the

brain in twenty-four; in three, no bacteria were obtained. The blood was positive in nine of the animals and negative in eighteen.

The streptococcus which produced chorea in the animals following intracerebral inoculation of small doses was similar to the streptococcus which I isolated in 1910 and have isolated from time to time since, and which sometimes produced chorea-like symptoms on intravenous injection of large doses. The colonies produced on blood-agar were small, dry, slightly elevated and nonadherent and were surrounded by a brownish green zone. After incubation for forty-eight hours, a narrow zone of hemolysis peripheral to the greenish zone often developed. The organism produced a diffuse or slightly granular growth in glucose broth and glucose-brain broth. It was free from a capsule and was regular in size. It occurred in diplococcus forms, and the chains, of medium length, were made up of diplococci. The different strains produced acid in dextrose, lactose, saccharose and raffinose agar, but not in mannite, salicin or inulin. The fermentative power of the strain from Case 4 was tested as isolated from the brain after one, two and three animal passages in rabbits and from the teeth of the dogs three months after devitalization and after from three to fourteen subcultures. The streptococcus from chorea was only slightly virulent on intraperitoneal and intravenous injection, but more virulent than most of the encephalitic strains on intracerebral inoculation. The power to produce chorea in animals was maintained through many culture generations, as high as the twelfth, by making the subcultures from four to six times a day, and through three animal passages, but was lost rapidly on aerobic cultivation on blood-agar plates.

A monovalent serum has been prepared in a horse by repeated intravenous injections, in increasing doses, of the strain from Case 4. Each of the strains isolated from the animals following intracerebral inoculation, and which had been kept under anaerobic conditions and in dense suspensions in glycerol and sodium chlorid solutions, was agglutinated specifically by this serum. Moreover, ten of fifteen strains of a similar streptococcus isolated from myoclonic and other forms of encephalitis were also agglutinated; whereas, five control strains of streptococci isolated from sources other than chorea and encephalitis were not agglutinated by this serum. The immunization is being continued with a mixture of choreic strains. Further immunologic experiments and the findings as to the protective power and therapeutic value of the serum will be reported later.

In one experiment on a dog, localization in the brain was facilitated by injecting sterile broth intracerebrally immediately after the pulps of four teeth had been removed and a dense suspension of the culture from Case 4 had been sealed in the canals. The animal died during

the night. Necropsy revealed numerous hemorrhages around the right lateral ventricle, and turbidity of the cerebrospinal fluid, due to leukocytes. A pure culture of the streptococcus introduced into the teeth was isolated from the cerebrospinal fluid.

Careful search for lesions in and around joints, muscles and heart valves was made in ten of the nineteen rabbits injected intracerebrally in Case 4. Three of the rabbits had hemorrhages and beginning endocarditis of the tricuspid or the mitral valves and lesions in the papillary muscles at the tendinous end, and four had lesions of fascial layers in muscles and around joints.

In view of these findings, four young rabbits were injected intravenously with the streptococcus from Case 4 in the second animal passage, two receiving 3 c.c. and two 5 c.c. of glucose-brain broth cultures. The rabbits were anesthetized in from three to five days. All had lesions of muscles, joints or heart valves. In one, only a few lesions of muscles developed, and in another, lesions of muscles and ligaments around the knee joints. The other two became lame in the

Localization of Chorea and Other Streptococci Following Intravenous Injection

Strains	Number of Animals Injected	Incidence of Localization in			
		Brain	Heart Valves	Joints or Muscles	Stomach
Chorea (1)	9	6	6	5	1
Epidemic encephalitis (3)	12	9	1	1	2
Epidemic hiccup (2)	8	3	0	0	0
Ulcer of stomach (5)	28	0	2	3	23

hind extremities, and necropsy disclosed turbid joint fluid in both knee joints, and beginning embolic endocarditis. One area of endocarditis was found along the line of closure of the mitral valve, and one at the base of the chordae tendineae in the right ventricle. No symptoms referable to the nervous system developed in any of the four rabbits, but microscopic examination revealed perivascular and other infiltration, chiefly by leukocytes, and focal hemorrhages.

This tendency of the chorea strains to involve heart valves, joints, and muscles as well as the brain was much more marked than that of strains of streptococci from other sources. In the accompanying table, I have summarized the results in animals injected intravenously with equivalent doses of different strains, freshly isolated, and in which the examination (gross, microscopic or cultural) was sufficiently complete to determine whether or not localization occurred in brain, heart valves, joints or muscles, and stomach. The tendency of each strain to localize in these animals in structures corresponding to those commonly involved in these diseases in man is well brought out, and is in keeping with the general results of my other studies on elective localization.

ILLUSTRATIVE EXPERIMENTS FOLLOWING INTRACEREBRAL INOCULATION

EXPERIMENT 1.—Rabbit 2356, weighing 890 gm., was injected intracerebrally, March 13, 1921, with 0.1 c.c. of a 1:100 dilution in sodium chlorid solution of the primary culture in glucose-brain broth of the tonsil pus from Case 1. The following day, the animal was extremely shaky, tremulous and ataxic, and was scarcely able to walk on account of peculiar contractions of the muscles of the extremities. Its head was extremely wobbly. When carrot was held to its mouth, the movements of the head became violent; but after the animal had succeeded in biting off a piece, which it ate with relish, the movements became less marked; yet they recurred each time an attempt was made to bite off pieces.

March 15, 16 and 17, the animal's condition was practically unchanged. The carrot test was repeated frequently. March 18, the animal appeared quite well, was alert and sat quietly in the cage; but when it hopped, its head became extremely wobbly and was thrown backward and from side to side in a peculiar rhythmic manner. On account of similar purposeless movements of the

Figure 3

Figure 4

Fig. 3.—Lesions in the brain of Rabbit 2356 (see protocol).

Fig. 4.—Lesions in the brain of Rabbit 2356 (see protocol); hematoxylin and eosin; × 100.

extremities, it could scarcely maintain its balance. March 19, marked weakness had developed, but otherwise there was little change. March 21, the weakness was less marked. The animal sat quietly in the cage, with head usually retracted, but when it attempted to hop, its head became wobbly and was thrown in all directions, and irregular contractions of the muscles of the extremities developed, causing the rabbit to fall to either side. The condition remained unchanged during the next two days, and the animal was found dead, March 24.

No gross lesions were found. Cultures from the emulsion of the brain and the spinal fluid yielded countless numbers of the characteristic streptococcus; those from the blood, a few colonies.

Sections revealed marked leukocytic and round-cell infiltration in a sharply circumscribed area surrounding the point of inoculation; slight round-cell infiltration in the pia, most marked surrounding the vessels (Fig. 3), and several areas of marked perivascular infiltration in the subcortical region (Fig. 4) and

in the cerebellum. Many diplococci were demonstrated in the area of marked infiltration at the point of injection, and a few in or adjacent to the other areas of infiltration (Fig. 5*a* and *b*). Two other rabbits injected with the same culture developed a similar train of remarkable symptoms.

EXPERIMENT 2.—Rabbit 3728, weighing 1,600 gm., was injected, June 30, 1922, with 0.2 c.c. of the salt solution suspension of the nasopharyngeal and tonsillar swabs from Case 4. July 1, at 7 a. m., the animal appeared excitable and hyperirritable, and had occasional twitching of the muscles of the fore extremities. At 9:30 p. m., it sat quietly humped up in the cage. When it was prodded, marked irregularly timed jerky movements of the head and extremities developed. July 2, it was excitable, turning its head from side to side, and often throwing it backward. Choreiform movements developed. During the following eight days, the condition remained much the same. July 11, it sat quietly in the cage most of the day, but on slight exertion it threw its head backward and from side to side. When prodded, its movements often became progressively worse, until it fell to either side, regaining its balance with some difficulty.

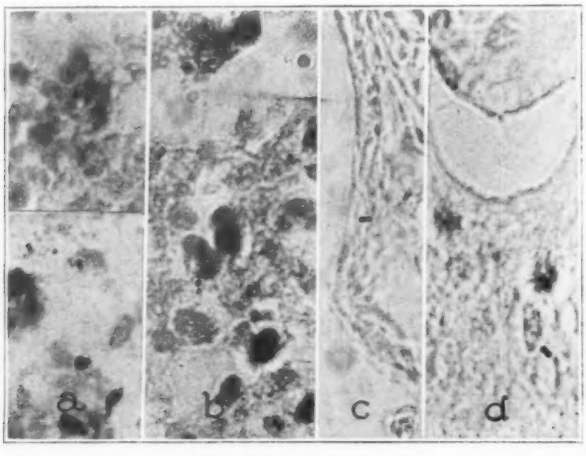

Fig. 5.—Diplococci in lesions of brain of rabbits: *a* and *b*, Rabbit 2350; *c*, Rabbit 3728; *d*, Rabbit 3764 (see protocols); gram stain; × 1,000.

There were no tremors nor spasms, and respiration was normal. The animal was chloroformed for examination. The vessels of the pia were congested; the cerebrospinal fluid was clear, but increased in amount, and the joints, muscles, myocardium and heart valves were normal.

Cultures from the blood were sterile; those from the brain yielded a few colonies of the characteristic streptococcus. Sections revealed perivascular infiltration in the subcortical region of the cerebrum; localized areas of slight infiltration in the pia, and an occasional diplococcus adjacent to dilated capillaries in the pia (Fig. 5*c*.)

EXPERIMENT 3.—Rabbit 3782, weighing 1,100 gm., was injected, July 18, 1922, with 0.1 c.c. of a 1:100 dilution in sodium chlorid solution of the culture from the brain of Rabbit 3728, in the fourth subculture. July 19, at 8 a. m., the animal appeared well. At 12 m., it had developed peculiar movements of the head, associated with vertical nystagmus, and irregular contractions of the muscles of the extremities which made it lose its balance at times. July 20, the choreiform movements of the head were less marked, but its head was slightly retracted and turned to the left. July 21, at 7 a. m., the animal was found dead.

Necropsy revealed extreme congestion of the vessels of the pia over the cerebrum; edema of the pia at the posterior junction of the medulla and cerebellum; marked cloudy swelling of the myocardium; large hemorrhages of the tricuspid valves, numerous large and small hemorrhages of the papillary muscles of the left ventricle, most marked at the apices; subendocardial hemorrhages in the septal wall of the left ventricle; nodular endocarditis of the mitral valve at the juncture of the chordea tendineae with the leaflet; several small subendothelial hemorrhages in the mitral valve (Fig. 6), and whitish lesions in the flat muscles of the lower abdomen and in the tendinous ends of muscles and ligaments around the left knee joint.

Cultures from the brain yielded a moderate number of colonies of the streptococcus; those from the blood, a few colonies. Cultures from the joint fluid, bile, liver and muscles remained sterile. Sections of the heart valves gram stained revealed a few diplococci in the hemorrhagic and nodular lesions of the mitral valve.

Fig. 6.—Subendocardial edema, *a*, and hemorrhage, *b*, in the mitral valve of Rabbit 3782; hematoxylin and eosin; × 100.

Experiment 4.—Rabbit 3764, weighing 1,810 gm., was injected, July 15, 1922, with 0.1 c.c. of a 1:10 dilution in sodium chlorid solution of the four-hour glucose-brain broth culture of the strain from the brain of Rabbit 3728 in the twelfth subculture. July 16, at 8 a. m., the animal was tremulous and ataxic; when standing, its whole body shook; and when it hopped, it tended to lose its balance, always falling to the left. At 12 m., the condition was much the same, but irregularly timed contractions of the muscles of the extremities, of varying intensity, had developed. At 6:30 p. m., the contractions of the muscles were worse, and, on exertion, choreiform movements of the head and the fore part of the body developed. July 17, there were extreme choreiform movements of the extremities. The animal became extremely ataxic and weak, and died.

Necropsy revealed marked congestion of the vessels of the meninges; localized hemorrhages of the pia over the lateral aspects of the cerebellum; edema of the pia over the posterior aspect of the cerebellum and medulla; hemorrhages of the tricuspid and mitral valves along the line of closure; one small hemorrhage at the base of the mitral valve, and an increase in the amount of cerebrospinal fluid, which was moderately turbid.

Cultures from the blood, kidney, liver and spleen were negative; whereas, cultures from the brain yielded a moderate number of colonies of the characteristic streptococcus.

Sections of the brain revealed moderate infiltration of the pia by leukocytes and round cells; slight perivascular infiltration in the subcortical region of the cerebrum, and marked invasion and infiltration of the cerebellar cortex by leukocytes (Figs. 7 and 8). Sections which were gram stained revealed a moderate number of diplococci in the areas of infiltration and in the adjacent tissues (Fig. 5*d*).

EXPERIMENT 5.—Rabbit 3755, weighing 1,900 gm., was injected intracerebrally, July 12, 1922, with 0.1 c.c. of a 1:1,000 dilution in sodium chlorid solution of the glucose-brain broth culture of the strain from Case 4, after two animal passages and in the second subculture. Blood-agar plate culture of the suspension injected yielded a pure growth of the green-producing streptococcus. July 13, at 12 m., the animal appeared well, but was somewhat wobbly, and when it hopped the fore part of the body tended to bob up and down. At

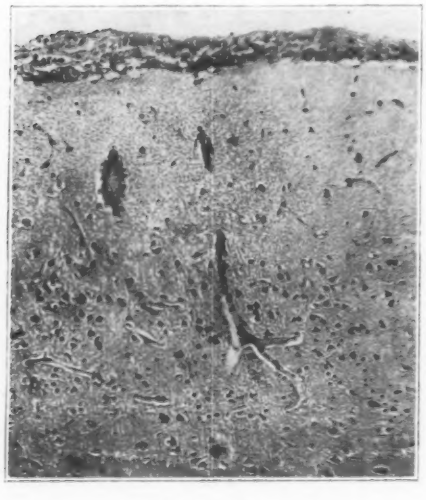

Figure 7

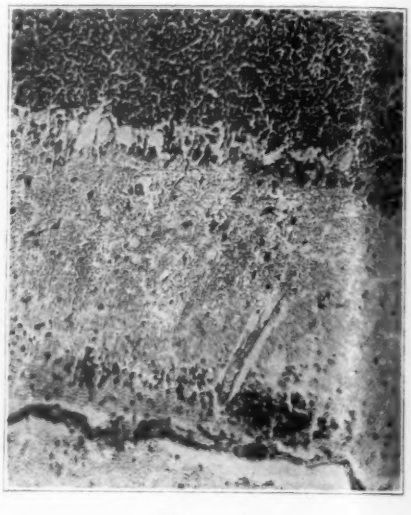

Figure 8

Fig. 7.—Moderate infiltration of pia over cerebral cortex; slight perivascular, and no parenchymatous infiltration (Rabbit 3764); hematoxylin and eosin; × 100.

Fig. 8.—Marked parenchymatous infiltration of cerebellum of Rabbit 3764; hematoxylin and eosin; × 100.

10 p. m., the fore part of the body bobbed more markedly, but more irregularly when the animal hopped, and peculiar choreiform movements of the head had developed. July 14, 15, 16 and 17, its condition remained about the same. In the interval from July 18 to July 27, the peculiar motions of the head and the bobbing of the fore part of the body became much less marked, and the animal appeared well when it was chloroformed, July 27. No gross lesions were found in the brain or the cord.

Cultures from the blood and the brain remained sterile. Cross-sections of the middle portion of the cerebellum revealed moderate localized perivascular round-cell infiltration of the pia (Fig. 9), and occasionally around the blood vessels within the substance of the cerebellum. In some instances, the infiltra-

tion was limited to that part of the vessels adjacent to the brain. Cross-sections of the posterior part of the right cerebellar hemisphere revealed a localized area of infiltration near the third ventricle, and a longitudinal section of the left cerebral hemisphere near the median line revealed an area of considerable size in which there was diffuse parenchymatous and perivascular round-cell infiltration (Fig. 10). In one vessel in this area, the lumen was almost occluded by infiltration with round cells within the wall of the vessel. No infiltration was found in the pia over the cerebellar cortex. There was no lesion at the point of inoculation, and none in the medulla.

The gross and microscopic findings in the central nervous system following intracerebral inoculation varied greatly, depending on the virulence of the strain, the amount of the culture injected and the resistance of the animals. In the animals that died soon after inoculation, moderately turbid cerebrospinal fluid and congestion of the vessels of the meninges were usually found, and occasionally localized hemorrhages in the pia. Aside from an occasional area of infiltration at the point of inoculation, gross lesions in the brain or cord substance and suppurative meningitis were not found. Sections showed a widespread but

Figure 9

Figure 10

Fig. 9.—Localized perivascular infiltration of pia at *a*, in cerebellum of Rabbit 3755; hematoxylin and eosin; × 100.

Fig. 10.—Parenchymatous infiltration in the cerebrum of Rabbit 3755. This lesion is similar to those shown in Figures 2 and 13; hematoxylin and eosin; × 100.

usually relatively slight leukocytic infiltration of the pia, most marked over the cerebral cortex; and at times, leukocytic and round-cell infiltration of the choroid plexus. In the animals that died late or were chloroformed for examination, evidences of diffuse meningitis were usually absent, and, as a rule, no gross lesions were found. Microscopic examination often revealed localized and perivascular infiltration in the pia (Figs. 3 and 9), and localized (Fig. 10) and perivascular infiltration, chiefly by mononuclear cells, in the subcortical region, in the pons, in the cerebellum and not infrequently in the choroid plexus. The degree of involvement was often directly proportional to the severity of symptoms, and the location of the most pronounced microscopic changes corresponded to that indicated by particular symptoms noted during life.

RESULTS FOLLOWING INFECTION OF TEETH IN DOGS

Since the tendency of this strain to localize in a characteristic manner was so marked on both intravenous and intracerebral inoculation, it was thought worth while to determine whether localization would also occur through foci of infection, thus simulating the condition in the patient from whom this strain was isolated, and in whose tonsils foci of infection were found. Accordingly, the cuspids in each of four healthy, active dogs were sterilized. A rubber dam was applied; and, after the ends of the teeth were cut off, they were reamed with

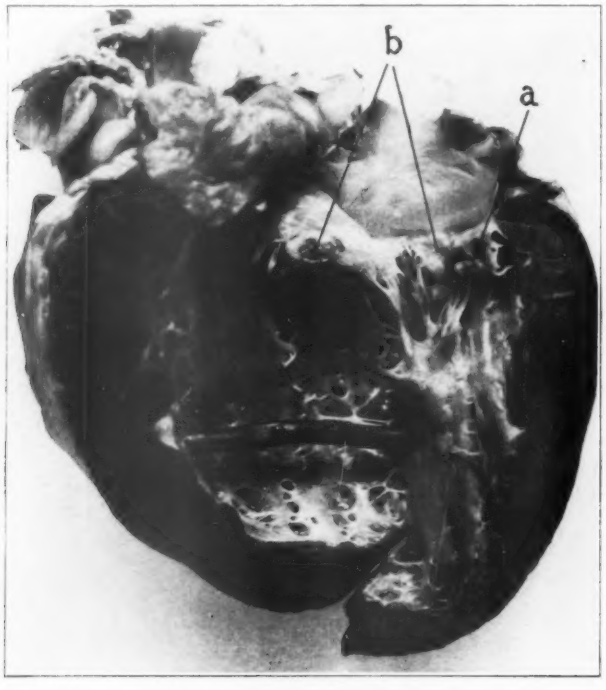

Fig. 11.—Nodule, *a*, and vegetations, *b*, endocarditis of mitral valve in a dog injected intravenously with the streptococcus from Case 4.

dental burrs; the pulps were extracted under intratracheal ether anesthesia; a dense suspension of a mixture of the actively growing streptococcus in the first, second, and third animal passages was inoculated into the canals, and the openings were sealed with dental cement. A part of the suspension of the streptococcus used to infect the teeth of these dogs was injected intravenously into two dogs. Six days after injection, one of the dogs developed rhythmic contractions of the muscles of the left shoulder and the left leg, which lasted for about a week. The animal was chloroformed seventeen days after injection.

Necropsy revealed a chocolate-colored edematous infiltration along the base of the mitral valve. The other dog appeared sick on the third day after injection. For several days, it protected the right foreleg, as if it were painful. It seemed prostrated, and when made to walk became short of breath. No symptoms resembling chorea developed. The animal was chloroformed eighteen days after injection. Necropsy revealed a firm, elongated, hemorrhagic vegetation (3 by 5 by 7 mm.) of the posterior leaflet of the mitral valve, originating along the line of closure (Fig. 11); an area of thickening with ulceration along the line of closure of the anterior leaflet, directly opposite another vegetation on the posterior leaflet (Fig. 11), and several subendothelial nodules nearer the base of the posterior leaflet of the tricuspid valve.

Fig. 12.—Areas of rarefaction at the apices of the roots of the lower cuspids of the dog that developed chorea following devitalization and infection of the teeth with the streptococcus from Case 4.

The strain inoculated into the devitalized teeth had retained specific infecting power over a period of three months.

Sections through the vegetations on the mitral valve revealed moderate leukocytic infiltration in and around the base of the fibrin deposit, in which a few cells, chiefly leukocytes, were found. No microscopic lesions were found in the myocardium.

Two of the dogs whose teeth were devitalized and infected remained well, while two developed muscular movements resembling chorea. In one, marked shivering spells and rapid twitchings of the muscles of the fore and hind legs developed the following day. This continued for about three weeks, when complete recovery ensued.

The findings in the other dog were as follows: The day after inoculation (July 25, 1922), the animal appeared nervous, and there

was repeated contraction of the left foreleg and the muscles of the fore part of the body, which it tried to control by crouching to the floor of the cage. The following day, it blinked frequently; the condition in the left foreleg had become more marked, and the animal still tried to control the muscular contractions, by lifting the leg from the floor and by crouching to the floor. This condition remained unchanged for three weeks, following which the muscular contractions gradually grew less marked; but they were still present, September 4, when the animal was chloroformed. There was no loss in weight. The devitalized and infected teeth were discolored, but firmly in place. There was no swelling opposite the roots. Roentgenograms of the lower jaw revealed decided areas of rarefaction around the root apices (Fig. 12).

Fig. 13.—Area of parenchymatous and perivascular infiltration in the subcortical area of the middle rolandic region of dog referred to in Figure 12; hematoxylin and eosin; × 100.

The pulp chambers were filled with thick chocolate-colored pus, in which large numbers of diplococci and streptococci were found, and from which the inoculated streptococcus was isolated in large numbers, together with a few gram-negative bacilli. The vessels of the meninges appeared congested. The cerebrospinal fluid was clear, but increased in amount. There were no gross lesions of the brain, but a small area of hemorrhagic infiltration was found in the posterior leaflet of the mitral valve.

The blood and brain yielded pure cultures of the streptococcus resembling the one isolated from the infected teeth. Microscopic examination of sections of the brain revealed areas of slight localized and perivascular infiltration in the pia over the cerebrum and cerebel-

lum; small hemorrhages in the subcortical region, often surrounding small vessels, associated with leukocytic infiltration; several areas of parenchymatous and perivascular round-cell infiltration in the subcortical region of the cerebrum (Fig. 13) and in the pons, most marked near the median line just anterior to the cerebellum (Fig. 14), and moderate neurophagocytosis surrounding the areas of perivascular infiltration. By far the largest portion of the sections examined were free from lesions. Painstaking search for bacteria revealed a few gram-positive diplococci in, and adjacent to, the fresh perivascular hemorrhages, with slight leukocytic infiltration. No bacteria were demonstrable in the areas of pronounced round-cell infiltration, nor in the normal tissues.

Fig. 14.—Area in pons in region of cerebellar peduncles showing perivascular round-cell infiltration in dog referred to in Figure 12; hematoxylin and eosin; × 100.

The strain isolated from the brain of this dog was injected intravenously into three rabbits, 1 c.c., 3 c.c., and 5 c.c., respectively, of the glucose-brain broth culture, in the second generation. The strain from the blood was injected intravenously into two dogs, after 2 c.c. of normal horse serum had been injected intracerebrally to facilitate localization. The rabbits remained free from symptoms and were chloroformed for examination three days after injection. The one receiving 5 c.c. showed no lesions. The one receiving 3 c.c. had hemorrhagic lesions on the inner and anterior aspect of each tibia, and the one receiving 1 c.c. had small hemorrhages in the posterior leaflet of the mitral valve. One of the dogs developed twitchings and irregular contractions of the muscles of the neck and of the left leg,

two days after injection. This lasted for several days, then disappeared, and the dog remained apparently well. When it was chloroformed fifty-two days later, no lesions were found. The other dog remained free from symptoms, and was chloroformed one week after injection. Necropsy revealed edema; nodular thickening along the line of closure of the mitral valve, and hemorrhages between the cusps of the aortic valves and in the papillary muscles. The tricuspid and semilunar valves were free from lesions.

The streptococcus inoculated into the pulp canals was isolated from one or more teeth in each dog when they were chloroformed, three months later. Roentgenograms of the lower jaw in the two dogs that remained well were negative; whereas, in the two that developed chorea-like symptoms, small areas of rarefaction filled with granulation tissue had developed (Fig. 12). The blood and brain were found sterile in the three that were free from symptoms when chloroformed.

SUMMARY AND CONCLUSIONS

Characteristic localization followed intravenous and intracerebral inoculation as well as the infection of teeth in dogs. The lesions were due to the same streptococcus, regardless of the fact that mixtures of bacteria in the suspensions and primary cultures were sometimes injected. The property on which specific localization depended was retained through three successive animal passages, after many rapidly made transfers of pure cultures, and for as long as three months in the teeth and brain of the dog. The specificity as regards both the infecting power and the immunologic properties was lost after ordinary aerobic cultivation. The symptoms produced were strikingly like those in chorea in man. The experimental lesions in the central nervous system, aside from a low grade meningitis, resembled in type and location the lesions in human beings as described by various observers, and were found chiefly within or adjacent to motor centers or motor paths in the cerebrum, in the midbrain and in the cerebellum. The extent and location of the lesions often corresponded to the severity and type of symptoms observed during life. Moreover, the lesions in the heart valves resembled those noted in chorea in man, in location, in gross appearance and in microscopic findings. The organism was demonstrated in, or adjacent to, the lesions, and proved absent in normal tissues on microscopic examination. The symptoms paralleled those noted clinically in type and degree; and, in the experiment on the teeth in dogs, in which the condition in patients was most closely simulated, in duration as well.

Many similar experiments which serve as controls were performed with strains isolated from cases of encephalitis, epidemic hiccup and

ulcer of the stomach (as summarized in the accompanying table), and also from the throats of normal persons, and persons suffering from poliomyelitis. In these experiments, localization rarely occurred in heart valves, joints or muscles; and except in myoclonic types of encephalitis, the lesions in the central nervous system did not induce symptoms like those following injection of strains from chorea.

In view of these results and the findings reported by others, the conclusion that chorea is due to a streptococcus having peculiar neurotropic, immunologic and other properties seems warranted.

BIRTH HEMORRHAGE INTO THE SPINAL CORD WITH RESULTANT BLADDER AND KIDNEY COMPLICATIONS *

REPORT OF A CASE

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Cases of birth hemorrhage into the spinal cord, though they probably occur more frequently than is generally supposed, are not numerous in the literature. Most work on the subject has been done quite recently.

The most comprehensive article on this condition is that of Crothers,[1] who quotes Head and Riddoch [2] at some length. These investigators studied the effect of cord injuries in young men wounded during the World War, and they conclude that high physiologic transections of the cord in healthy young men run the following course:

First stage: There is muscular flaccidity, with a lack of tone in the skeletal muscles, anesthesia, dryness of the skin, which is easily marred, and retention of urine and feces.

Second stage: After a few weeks, reflexes appear. At first, stimulation of the sole causes various toe movements; later, a variety of flexion responses of the legs and lower abdomen can be elicited. With severe stimulation, both legs and recti abdominis share in a vigorous "mass" reflex which is accompanied by evacuation of the bladder. The easy elicitation of this "mass" reflex, accompanied by sweating, is characteristic of this stage of reflex activity. Tendon jerks and other signs of extensor excitability are later signs. The bladder action becomes "automatic," the organ emptying itself at definite degrees of pressure without other stimulation, or at lower pressures when the mass reflex is elicited.

Third stage: As sepsis of serious importance intervenes, the reflex activity subsides, and sometimes never returns. Obviously, sepsis occurring prior to the second stage may prevent the occurrence of reflex activity of any kind.

Crothers quotes several authors, notably Ruge, Warwick and Stoltzenburg, to show that babies dying of asphyxia shortly after breech delivery give evidence of cord injury in a considerable per-

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* From the department of Pediatrics of the Duluth Clinic.

1. Crothers, Bronson: Injury of the Spinal Cord in Breech Extraction as an Important Cause of Fetal Death and of Paraplegia in Childhood, Am. J. M. Sc. **165**:94-110 (Jan.) 1923.

2. Head, H., and Riddoch, G.: Brain **40**:188, 1917.

centage. He deems it likely, in the light of the work of Head and Riddoch, that, if such babies survive, they will show a high degree of reflex excitability, provided the lesion is not high enough to involve the medulla or phrenic nerves or low enough to destroy the lumbar enlargement. Under favorable circumstances, indefinite existence seems quite possible. Crothers cites five cases of his own, in which the ages ranged from 2 weeks to 12 weeks. All of these cases gave a history of breech delivery. He draws the following conclusions:

1. High cervical transections of the cord are probably all fatal on account of the proximity of the lesion to the phrenic nerves and the medulla.

2. Transection below this fatal level, if accompanied by enough hemorrhage to destroy the cells of the lower segments, results in anesthesia and permanent flaccidity.

3. Transection confined to a few segments and not involving the lumbar enlargement will show, in succession, the following symptoms: (*a*) Anesthesia with flaccid paralysis. After a few days or weeks, the flaccid paralysis will be modified and the infant will show (*b*) anesthesia as before, a zone of flaccidity corresponding to the destroyed anterior horn cells, and below this zone reflex activity of distinctive type. During this stage, the action of bladder and rectum becomes automatic. On theoretical grounds, it seems likely that this stage of reflex activity will last only so long as severe infection is avoided.

4. It is evident that the vast majority of obstetric spinal cord injuries are incident to maneuvers in breech extractions. He considers the high percentage of this condition following breech extraction due to the following factors peculiar to this type of presentation: (*a*) Traction exerted over the entire length of the spinal column. (*b*) Pressure on the head, resulting from intra-uterine contraction or due to suprapubic pressure by the operator or assistant. The spinal cord of the baby is firmly anchored below by the cauda equina and above by short, heavy, almost horizontal, spinal roots. Its upper end is continuous with the medulla. When the spinal column becomes elongated through traction, one or two possible accidents may occur. The cord may give, with resultant hemorrhage and even rupture, or it may hold and pull down the structures above so that fatal herniation of the medulla into the foramen magnum may result. Death in this case, Crothers considers due to increased medullary pressure, resulting in vasomotor collapse; or to extreme vagus stimulation.

The work of Crothers is of great importance and, though based on theory to a great extent, as he admits, gives us a new point of view and should stimulate further investigation.

Kooy [3] reports the case of a child born by version, in which there was nearly complete rupture of the cord at the level of the ninth and tenth thoracic segment. The child lived for nine years, with almost complete anesthesia; incontinence of urine and feces, and spasticity of the legs. Microscopic examination of the cord postmortem revealed practically complete destruction at the above mentioned level, the only long tract left intact being the ventral pyramidal tract.

Burr [4] reports two cases of hemorrhage into the spinal cord at birth following breech delivery. The first was seen at the age of 4½ months. Necropsy demonstrated practically complete destruction of the lower cervical cord. The child's head was pulled back; there was the characteristically flexed position of the upper arm and forearm; the breathing was entirely diaphragmatic, and there was palsy of the thoracic and abdominal muscles and flaccid palsy of both legs. In the second case, the child was seen at the age of 3 months. The findings were quite similar to those in the first case. The child died and there was no necropsy. Both of these births were breech deliveries.

Burr quotes Spencer, who performed a series of necropsies on 130 fetuses, the majority still born, in which the spinal cord was examined in forty-four cases. In thirty of these forty-four cases, there was hemorrhage somewhere within the spinal canal; and, of these thirty cases, it was within the spinal cord in six. From his statistics, Spencer concludes that spinal hemorrhage is greatly favored by presentation of the lower extremity. He thinks the increased liability to hemorrhage is due partly to the great pressure on the soft parts, with resultant driving of the blood to the central organs, and partly to the fact that traction is sometimes employed. Spencer regards the normal delicacy of the fetal blood vessels as the one essential feature in the causation of hemorrhage.

Burr considers the cause of the hemorrhage in his case, which came to necropsy as most likely due to rupture of overfull vessels from pressure on the soft parts during birth.

Leavitt [5] reports a case of spinal cord hemorrhage in a child born by breech extraction, with flaccid paralysis below the site of hemorrhage; characteristic position of the arms, and flaccid paralysis of the chest and abdominal muscles, and sphincters of bowel and bladder.

I observed the subjoined case of hemorrhage into the cervical cord, at birth and at frequent intervals thereafter until the child died, at the age of 9 months.

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3. Kooy, F. H.: J. Nerv. & Ment. Dis. **52**:1 (July) 1920.
4. Burr, C. W.: Hemorrhage into the Spinal Cord at Birth, Am. J. Dis. Child. **19**:473-477 (June) 1920.
5. Leavitt, F. H.: Arch. Pediat. **39**:758, 1922.

REPORT OF CASE

History.—G. K., was born, Feb. 19, 1922, of Greek parentage. The mother and father, were living and well. There had been no previous pregnancies, and there was no history of any chronic disease. The birth was a breech delivery, both feet presenting. Delivery was not unusually long, although the head was rather difficult to disengage.

Examination.—The child was seen by me the day after birth, when I made the following notes: "Weak cry, listless, cold, breathing practically all diaphragmatic."

For the next ten days, it was seen daily, the case running the following course: The child remained weak; the cry was poor, and the breathing was entirely diaphragmatic. The chest was pulled in and the abdomen ballooned. Pressure on the abdomen frequently resulted in urination. There was some

Fig. 1.—Patient at 3 months of age. The position of arms and hands, retraction of head and pulling in of chest are evident.

movement of the arms and legs. Sensation was not tested. Tension at the fontanel was normal. On the fourth day, coagulation time was twelve minutes (Rodda method); bleeding time, four minutes (Duke method). Spinal puncture performed on this day revealed a xanthrochromic fluid, there being numerous blood cells microscopically.

Treatment and Course.—The child was given three intramuscular injections of the father's blood, of from 15 to 30 cm. each, during the next few days. Spinal puncture on the sixth day again gave a xanthrochromic fluid. There was no evidence of bleeding elsewhere. While in the hospital, the baby became markedly icteric. On the ninth day, it was noticed that it held the arms close to the body, flexed at the elbow, and moved the forearms and hands fairly well. The icterus became less; the general condition improved, and the child was discharged from the hospital at the age of 2 weeks.

From this time on, it was seen at frequent intervals.

At 1 month, the paralysis of the intercostals was marked; the abdomen large, and the respiration was entirely diaphragmatic. The arms were held in a rather fixed position of flexion at the elbow, and dorsiflexion of the hands. The impression of hemorrhage into the cervical cord at birth was retained. Attempts to elicit changes in sensation were unsatisfactory.

The Wassermann reaction of the mother and of the child at 6 weeks of age were negative. A note at the age of 7 weeks says: "Legs limp, poor strength, knee jerks present."

At 2 months, the child became ill with fever. It was listless, and there was a tendency to hold the head back. Nystagmus was noted, with the quick component to the left. The pulling back of the neck was first noticed here, though probably present before, the head being set down on the shoulders. This condition continued through life. A roentgenogram of the cervical spine at this date revealed no definite abnormality. The child was sent to the hospital, where it remained for two weeks, running an irregular septic temperature due to a rhinopharyngitis and otitis media. Several urine examinations during this period revealed a few pus cells, insufficient, however, for a diagnosis of pyelitis. The child gradually recovered, and was sent home, where it did well for three or four weeks.

Fig. 2.—Spinal cord as removed at necropsy. There is degeneration in the cervical region, with adhesions to the dura.

At 3½ months, the child became febrile again, without ascertainable cause. The pupils were markedly contracted, and remained so thereafter. They responded slightly to light. For the next month and a half, there was intermittent fever. Finally, at 5 months, the urine was found to be full of pus, which was so thick that it was plainly visible in the bottom of the centrifuge tube. The bladder could be palpated almost up to the umbilicus through the thin, weak abdominal wall. Pressure on the abdomen invariably caused urination. At this time, elicitation of the knee jerks on one side frequently caused clonus of the opposite leg to appear. Vigorous treatment for the pyuria was at once instituted and was continued over a long period. Large amounts of water were given, and sodium bicarbonate and hexamethylenamin alternated. Several

injections of horse serum were given intramuscularly. Culture of the urine yielded colon bacilli. An autogenous vaccine was made and given over a period of several months. None of these methods were of any avail. The urine remained full of pus and continued so for four months, until the time of death. For most of this period, the child ran a septic temperature, frequently up to 103 or 104 F. The kidneys increased in size and could be easily palpated in either loin. It is remarkable that the child gained weight in spite of the severity of the infection.

At 8½ months, a severe rhinitis became manifest. This soon developed into the bronchopneumonia which caused death, at the age of 9 months.

Necropsy Findings.—The general appearance was as during life: the abdomen large; the chest pulled in; upper arms close to the body; forearms flexed at the elbow; hands dorsiflexed at the wrist.

Fig. 3.—Section of urinary system. There is dilatation of the ureters and pelves, and hemorrhagic inflammation of the bladder wall.

Thorax: The heart showed no anomalies. The thymus was normal in size and appearance. In the lungs, there were numerous areas of consolidation in all lobes.

Abdomen: The gross appearance of all organs except the urinary tract was normal. The kidneys appeared larger than normal. They were mottled grayish red, and the surface showed fetal lobulations. The ureters on either side are equally enlarged, the diameters being about 1 cm. The increase in diameter was uniform from the pelvis to the bladder wall. Section of the kidneys revealed that the pelves were dilated; the surface of the pelves had a rather thickened, granular appearance. The walls of the ureters appeared thickened and ragged. The parenchyma of the kidneys was softer than normal. Section of the bladder showed that the wall was thickened, and the surface was thrown into numerous rugae, which were red and inflamed. The ureteral openings appeared normal. A tiny probe could be passed into each ureter with-

out difficulty. There was no apparent obstruction at the bladder wall or above. The bladder, ureters, and pelves contained a large amount of free pus diluted with urine.

Permission being granted only to remove the cord, as much as could be reached from below was dissected away. Gross examination of the cord revealed that the cervical region, as high up as it was removed, consisted of only a small column of tissue, scarcely half the size of that portion of the cord below. This apparently contained little or no nervous tissue, and appeared to be fibrous. It adhered tenaciously to the dura mater. Below this level, the cord appeared practically normal.

Sections of the organs were sent for microscopic study to Dr. E. T. Bell of the pathologic department, Minnesota University Medical School, who reported: "Section of the cord at the site of the lesion shows complete degeneration of all tracts. Below this level there is marked degeneration of the pyramidal tracts, especially in the crossed pyramidals. The kidney shows hydronephrosis, with chronic pyelonephritis. The ureters are dilated, and show practically no disease. There is a low grade, chronic inflammation of the mucous membrane of the bladder. The condition of the urinary tract is evidently due to the spinal cord lesion, with subsequent infection."

At Dr. Bell's suggestion, a section of the cord was sent to Dr. Ernest Sachs, neurologic surgeon to the Washington University Medical School, who reported: "The section shows degeneration of the direct and crossed pyramidal tracts. The lateral portion of the cord is not myelinated, and both the dorsal and ventral cerebellar tracts are involved, the dorsal less so than the ventral. The order of myelinization of these tracts is: ventral, dorsal, pyramidal, and in a child of 9 months, the dorsal tract should be myelinated, which it is not in this section. This may be explained by the hemorrhage at a higher level."

SUMMARY

1. In a case of hemorrhage into the cervical cord at birth, the child was born by breech extraction, some difficulty being encountered with the aftercoming head. The hemorrhage I consider due to trauma incident to delivery rather than to abnormal condition of the blood, in spite of a slight prolongation of the coagulation time. There were no evidences of hemorrhage elsewhere, as is the frequent finding in hemorrhagic disease of the new born. Spinal puncture on the fourth day of life revealed only old blood. The hemorrhage was evidently below the level of origin of the phrenic nerves as the diaphragm functioned normally. Necropsy revealed a complete degeneration of the cord in the lower cervical region and degeneration of various tracts at lower levels.

2. The child showed the typical picture of cervical cord injury. The position of the arms was characteristic. The breathing was entirely diaphragmatic, there being paralysis of the thoracic and abdominal muscles. The legs were paralysed.

3. As a result of bladder paralysis with back pressure, the child developed double hydro-ureters and hydronephrosis. Infection resulted in both bladder and kidneys. As would be expected, this infection did not respond to any treatment.

4. Movements of the legs were noticed a few days after birth. Knee jerks were elicited at 7 weeks, the response being weak, however. At the age of five months, attempts to elicit knee jerks on one side resulted in clonus of the entire opposite leg. No satisfactory sensory tests were obtained.

A FATAL CASE OF THRUSH INVOLVING THE SKIN, LUNGS AND NAILS*

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Thrush, as a generalized disease, is a rare condition, presenting not only points of unusual interest but also a baffling problem in treatment. Therefore, when one such case was seen and studied for a period of three years, it was considered of enough importance to be reported. A comprehensive search of the literature yielded only two references.[1]

REPORT OF CASE

D. W., a girl, born Jan. 16, 1917, weighing, at birth, 7 pounds (3,175 gm.), the youngest of a family of four girls, at the age of 5 months suffered an attack of bronchopneumonia complicated with cervical adenitis and otitis media. (The discharge from the ears persisted up to the time of death.) In March, 1919, the patient had an attack of influenza, which lasted a few days. In April of the same year, the mother noticed an inordinate amount of "drooling," with coated tongue and grayish white patches covering the mucous membrane of the mouth. A diagnosis of thrush was made at this time, and ordinary remedies were used without any appreciable change in the condition during the next six months. In the late summer, the child began to have frequent attacks of vomiting, accompanied by a very fetid odor of the breath.

From October, 1919, to February, 1920, she was kept on a diet consisting almost exclusively of vegetables and fruits. In November, 1919, it was noted that the index finger of the left hand had become infected. Shortly afterward, a brownish red spot, with a clearly defined outline, and covered with fine, branny scales, developed on the back of the neck. This at first was thought to be in the nature of ringworm, but scrapings from this area showed the characteristic *Oïdium albicans*. This rapidly spread until the entire scalp became involved, the eruption having much the appearance of a dry seborrhea.

Since none of the remedies previously used seemed to have any appreciable effect on the progress of the disease, the child was sent to Dr. W. P. Larson, professor of bacteriology at the University of Minnesota Medical School, with a request that he make a complete examination of the various lesions and endeavor to procure a vaccine. Scrapings taken from the mouth, skin and finger nails all showed *Oïdium albicans*. Washed sputum showed the same organism. The sputum was repeatedly subjected to a searching and exhaustive examination, the results always being the same. From these cultures, a vaccine was made. The patient received in all sixteen injections. A marked improvement in the clearing up of the mucous membrane of the mouth was apparent after the second injection, but the effect was not of long duration.

It was noted at about this time that the skin of the face was becoming involved. This condition gradually spread until, at the time of death, nearly the whole of the face was covered with the eruption; this, with eruptions on the entire scalp, the left hand, the nails of that hand, the back of the right

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* From the Miller Hospital Clinic and the Pediatric Department of the University of Minnesota Medical School.

1. Schamberg: Arch. Pediat., August, 1915, p. 617. Sasamoto: Jap. Ztschr. f. Derm. & Urol. **20**.

hand and wrist, and several areas on the chest and about the vulva, together with the chest findings, the cough and expectoration and the severe vomiting made a most distressing picture.

Various changes were made from time to time in the child's diet, but as none of these seemed to influence the condition in any way, she was allowed anything she wished. The eruption gradually extended over the entire left hand, the

Fig. 1.—Appearance of child shortly before death.

finger nails assuming a thickened, clawlike appearance. At times, the nails dropped off, only to be replaced by others of increased thickness.

During the summer and autumn of 1920, the condition progressed slowly. Vomiting became less frequent, though a more or less persistent cough had developed. Examination of the chest led to the belief that the thrush was gradually involving more of the lung tissue. For the next succeeding six months, little change was noted.

In June, 1921, the patient was taken to North Dakota for a visit. While there, she seemed to improve in general health, but the condition of the mouth and skin remained unchanged. About this time, the thrush appeared on the right wrist, spreading slowly upward and downward. The child, when seen on her return to St. Paul, September 1, weighed 28 pounds (12.8 kg)—her greatest weight. The skin condition had not improved.

Fig. 2.—Appearance of patient shortly before death.

October 10, she was taken suddenly ill with what was at first thought to be pneumonia, but what was probably an acute exacerbation following a fresh invasion of lung tissue by the advancing thrush. Recovery was slow, the cough persisting and at times causing much distress. A similar attack occurred about July 1, 1922. On two or three occasions, small quantities of bright red blood appeared after one of the more severe paroxysms of coughing. From this time on, the child grew gradually weaker, until death occurred, September 2, from exhaustion. Necropsy was not obtained.

COMMENT

The outstanding features of this case, aside from the severity of the skin eruption, were the very offensive odor of the breath in the early stages, suggestive of gangrene of the lung; the continuous vomiting and the harrassing cough, and the progressive emaciation and pronounced muscular weakness.

The treatment consisted in a trial of all the well-known remedies usually applied in thrush and, in addition, arsphenamin, iodids, the

Fig. 3.—Appearance of hands of patient shortly before death.

roentgen ray, mercurial inunctions and a vaccine prepared from scrapings taken from the various lesions. During the period of illness (two and one-half years), the child was seen by several of our confreres, and in every instance the laboratory findings confirmed the diagnosis. Wassermann, blood and urinary findings were always negative.

Figures 1, 2 and 3 show the condition as it existed shortly before the child's death.

PHYSIOLOGY OF EXERCISE IN CHILDREN.

PART 2. STUDY OF COLLAPSE IN NORMAL CHILDREN *

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In Part 1 of this study,[1] we presented the results of our investigation of the maximum physical capacity of normal schoolchildren and of the effect of maximum physical effort on the circulatory reactions.

It is the consensus of opinion among investigators that, in normal persons, after moderate amounts of exercise, there is always an increase in the pulse rate and in the systolic blood pressure. However, the opinions vary regarding the effect of exhaustive exercise on the circulatory reactions, especially in the event of collapse. A review of the extensive literature on this subject leaves one confused and in doubt. The reasons for this are: 1. No one has ever established a normal quantitative standard of physical capacity for work. This applies to adults as well as to children. 2. The technic employed lacks uniformity. 3. No careful and comprehensive attempts have been made, either by the physiologist or by the clinician, to compare the experimental data obtained in normal conditions with those obtained in diseased conditions.

In this paper, we attempt to answer the following questions.

1. What are the circulatory reactions in normal children who have surpassed the limit of their physical capacity?

2. What is the physiologic explanation of the curves described below?

3. What is the clinical significance of these curves?

Katzenstein,[2] in 1903, was among the first to study the systolic blood pressure and the pulse rate in fatigue resulting from prolonged muscular effort. He does not publish any curves, but he states as the general conclusion that the pulse rate and the blood pressure register a drop after cessation of exhaustive exercise. Heichelheim and Metzger,[3] in 1906, studied the circulatory reactions in twelve young

* Received for publication, June 29, 1923.

* From the Department of Pediatrics, University of Minnesota Medical School.

1. Seham, Max, and Egerer-Seham, Grete: Physiology of Exercise in Childhood, Part I, A Study of Normal Children of School Age, Am. J. Dis. Child. **25**:1 (Jan.) 1923.

2. Katzenstein: Ueber eine neue Funktionsprufung des Herzens, Deutsch. med. Wchnschr. **30**:807-809, 1904.

3. Baldes, Heichelheim and Metzger: Untersuchungen über den Einfluss grosser Körperanstrengungen auf den Zirkullationsapparat der Nieren und des Nervensystem, München. med. Wchnschr. **53**:1865-1866, 1906.

athletes, from 17 to 27 years of age, at the end of a 100 kilometer run at top speed. They claim to have found that the blood pressure was lowered 25 per cent. They omit the time of their readings; nor do they mention for how long a period after exercise they continued their determinations. Potter and Harrington,[4] in 1909, studied the effect of Marathon runs (from 10 to 20 miles) on young athletes. They, too, noticed a lowering of the blood pressure after the runs. Barach, in 1910, took blood pressure readings of athletes, 19 years of age, after Marathon runs. The average systolic blood pressure before the race was 126.5 mm., as against 107.5 mm. after the race. In every instance, there was a fall of the blood pressure below normal.[5] Lowsley, in 1911, investigated the effect on athletes of all types of athletics, from mild games to the most exacting Marathon runs. His work is most accurate and comprehensive. He observed that, after violent running, the blood pressure as well as the pulse rate drops precipitately, remaining below the preexercise level for long periods. In fatiguing, 6-mile runs, the subnormal phase persisted for from four to five hours. In 20-mile races, the men were carried off in a delirious and fainting condition. The first readings were taken from one-half to one hour after the race, but the pulse rate was so faint and the blood pressure so low that neither could be obtained. The average drop of the blood pressure after exercise was 24 mm.

In our study with the ergometer of the effect of exhaustive exercise on the circulatory reactions in normal schoolchildren, twelve of 110 children examined exceeded their limit of capacity in spite of all precautions taken. It was impossible by any methods to predict whether or not a child had reached the limit of its capacity. The circulatory reactions during exercise are not suggestive of overexertion. Thus, the opportunity presented itself to study sixteen cases of collapse in twelve children, thirteen occurring after exhaustive exercise on the ergometer and three, in two boys, after dumb-bell exercise. All of the children were perfectly normal, ranging high in weight, height and general muscular development. Three boys were 15 years old; three, 14; two, 13, and two, 12; and one was 11, and one, 9. The fact that there was a larger number of collapses in older children is probably to be laid to a greater spirit of competition. The subjective signs of collapse never occurred during exercise, but they became apparent after cessation of exercise, when practically all the boys were very

4. Potter, N. B., and Harrington, J. T.: Medical Supervision of Athletics Among Boys at Boarding School, J. A. M. A. **53**:1957-1960 (Dec. 11) 1909.

5. Lowsley: The Effects of Various Forms of Exercise on Systolic, Diastolic and Pulse Pressures and Pulse Rate, Am. J. Physiol. **27**:446-466, 1911.

dyspneic and covered with a profuse and general perspiration. Detailed information as to the technic was given in Part 1.

Every collapse manifested itself by nausea; in one case by vomiting. Two children complained of chills, and two others had a tremor of the entire body. In all subjects the heart sounds became so faint that they could scarcely be heard. In one child, a definite systolic murmur was audible at the apex for a period of five minutes; in another, a trigeminal extrasystole persisted until the blood pressure assumed the normal level. One child yawned continuously for about fifteen minutes after exercise. Fortunately, none of the children showed any untoward effects. Except for muscular fatigue, none showed any prolonged ill-effects. Only one child stayed away from school the following afternoon, all the others returning to their classes after a short period of rest. Race, physical development, height and weight had no bearing on the frequency of collapse. We were unable to detect clinical signs of acute dilatation, such as displacement of the apex beat to the left or an increase of the transverse diameter of the heart by percussion.

CIRCULATORY REACTIONS IN COLLAPSE RESULTING FROM EXHAUSTIVE EXERCISE

Blood Pressure.—The curves of the systolic blood pressure and pulse rate after cessation of exercise were so constant and striking that a detailed discussion of every case will be given. In every instance, the blood pressure dropped suddenly after cessation of exercise, the drop preceding nausea by from ten to 510 seconds. The subjective symptoms of collapse followed the objective circulatory signs. In nine of thirteen cases, the first exhibition of a sudden drop of blood pressure came within sixty seconds; in two, within two minutes, and in one, after five minutes. In all but two, the maximum rise was obtained on the first reading (in the majority of the cases at five seconds). In only three cases, the maximum rise occurred at ten, twenty and thirty seconds, respectively. In no instance did the blood pressure show a delayed rise. The maximum rise of blood pressure averaged 30 mm. In thirteen collapses, the blood pressure passed the preexercise level at an average of 155 seconds, the maximum being 330 seconds (Case 4) and the minimum twenty seconds (Case 12). The average difference between the preexercise level and the lowest subnormal reading was 16 mm., the highest subnormal reading being 40 mm. (Case 6), and the lowest 6 mm. (Case 3). These figures are not absolutely accurate because the readings had to be discontinued during the period of collapse. For the same reason, the reaction time of the blood pressure

could be determined in only three cases. Case 8 had a reaction time of 720 seconds, Case 9 of 600 seconds and Case 7 of 420 seconds.

The foregoing circulatory reactions in collapse are in striking contrast to the circulatory reactions exhibited by the same children after exhaustive exercise without collapse. Here, the maximum rise of blood pressure occurred on an average at twenty-one seconds, and in only two at five seconds. The average maximum rise of the blood pressure was 36.2 mm. Only one big drop of the blood pressure occurred, usually at the time of severe perspiration, and never did the blood pressure

TABLE 1.—*Findings in Case 1 (M. F.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	180	5	149	...
156	180	10	...	166
168	...	20	...	163
156	156	30	152	161
...	156	40	149	...
...	148	50	148	...
144	132	60	130	150
132	132	90	130	154
132	132	120	124	154
126	126	150	119	134
120	126	180	111	133
120	132	210	110	133
108	Heart sounds faint	240	104	127
108	...	270	Nauseated, collapse	118
108	...	300	...	115
108	...	330	...	114
108	...	360	...	115
108	...	390	...	110
108	...	420	...	107
102	...	450	...	108
102	...	480	...	108
...	...	510	...	...
...	...	540	...	...
...	...	570	...	...
...	...	600	...	...

* Preexercise pulse rate, 90 beats; preexercise blood pressure : collapse, 110 mm.; normal, 108 mm.

drop below normal. The reaction time of the blood pressure in Case 8 was 330 seconds as against 720 seconds in collapse.

Pulse Rate.—The drop of the pulse rate in collapse is not so striking as that of the blood pressure. In general, however, the pulse rate drops more suddenly in collapse than after exercise not followed by collapse.

REPORT OF CASES

CASE 1 (Table 1).—M. F., aged 14, a perfectly normal boy, had had no previous experience in bicycle riding and at first had difficulty in riding smoothly. On his first attempt, he rode 13,842 foot pounds. Although he was markedly tired and dyspneic, the pulse and systolic blood pressure after cessation of exercise came back to normal by the usual decline. A few days later, he rode at the top of his speed, averaging about 225 revolutions per minute. He then rode 45,690 foot pounds in eleven minutes. He collapsed 240 seconds after cessation of exercise. The contrast between the curve in collapse and

the one after severe exercise is very striking. Whereas in the normal curve[6] the heart could easily be heard, in the collapse the pulse became faint at 180 seconds and could not be counted even at the apex. The systolic blood pressure slowly descended after the ride of 13,842 foot pounds and returned to normal at 390 seconds; in collapse, however, it fell in jumps, the first drop being observed at ninety seconds (130 mm.) at which time, in the previous curve, it had reached only 159 mm. At 240 seconds, it had fallen to 104 mm., which is 6 mm. below normal. The readings had to be discontinued on account of nausea. When examined again at 480 seconds, the blood pressure had returned to the preexercise level, and the subject felt perfectly well.

Case 2 (Table 2).—H. P., aged 14, a slender boy, rode the bicycle twice. The blood pressure and pulse curves were normal after exercise of 20,730 foot pounds. He collapsed, however, after 22,176 foot pounds. Table 2 shows the difference in the blood pressure readings after the two experiments. In

Table 2.—*Findings in Case 2 (H. P.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	168	5	130	...
168	156	10	132	...
156	...	20	115	132
156	144	30	115	126
...	144	40		
156	Heart	50	Faint; water	126
156	sounds	60		126
144	weak	90	114	117
132	126	120	105	110
132	126	150	105	103
132	126	180	101	103
132	...	210	96	99
132	126	240	99	93
132	...	270	99	93
...	126	300	92	...
...	...	330	82	...
120	126	360	81	...
...	126	390	80	...
...	Heart sounds faint	420	Collapse	...
...	...	450	...	...
...	...	480	...	...
...	...	510	...	...
108	...	540	...	...
...	...	570	...	...
...	...	600	...	...

* Preexercise pulse rate: collapse, 72 beats; normal, 81 beats; preexercise blood pressure, 93 mm.

collapse, the blood pressure had dropped to 115 mm. at twenty seconds after cessation of exercise, as against 132 mm. in the other experiment. He complained of weakness; and he took a drink of water. After a second fall of the blood pressure, of 9 mm. at 120 seconds, the blood pressure descended slowly for 210 seconds, reaching the preexercise level at 300 seconds. In the following ninety seconds, it remained subnormal, the blood pressure having fallen 13 mm. below the normal reading. The boy was uncomfortable and felt nauseated, and the experiment was discontinued.

Case 3 (Table 3 and Chart 1).—M. S., aged 12, was a sturdy boy of great endurance. The curves in Table 4 are typical of the circulatory reactions after exhaustive exercise and in collapse. The dotted lines represent the pulse and blood pressure curves after exercise of 25,452 foot pounds. No bad after-

6. For convenience, curves of circulatory reactions after severe exercise, not followed by collapse will be referred to as "normal curves."

TABLE 3.—*Findings in Case 3 (M. S.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	...	5	128	...
...	...	10	135	120
...	...	20	137	130
...	...	30	138	128
...	...	40	127	129
...	...	50	...	133
...	...	60	126	127
135	136	90	...	124
...	...	120	90	116
...	...	150	...	110
120	...	180	100	102
...	...	210	...	104
...	...	240	101	105
...	114	270	105	103
120	...	300	96	106
...	...	330	96	104
...	...	360	98	102
...	...	390	100	100
120	108	420	...	100
...	...	450	100	...
120	108	480	101	97
...	...	510	105	94
120	102	540	101	96
...	...	570	...	93
120	108	600	103	96

* Preexercise pulse rate, 88 beats; preexercise blood pressure: collapse, 101 mm.; normal, 97 mm.

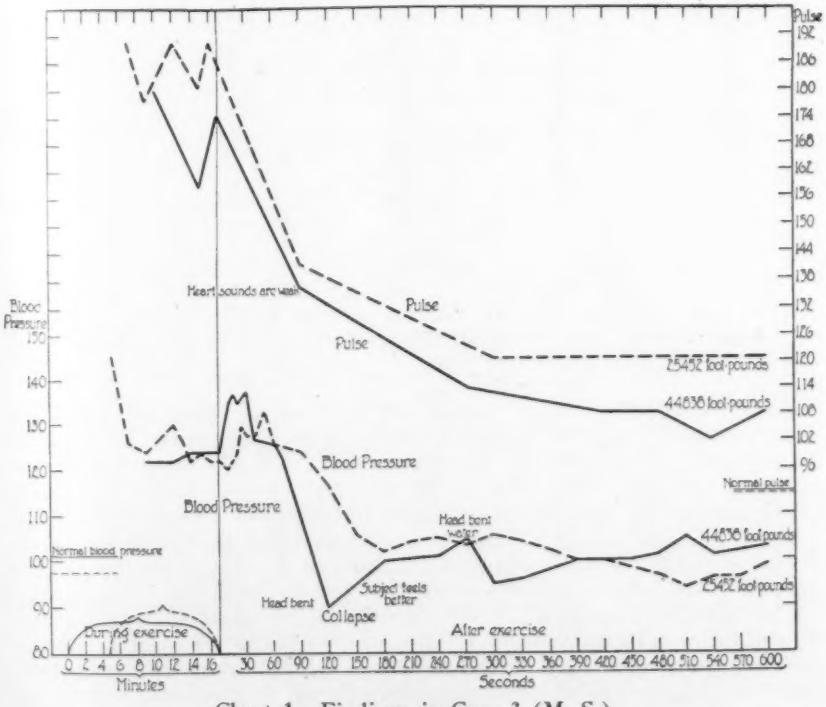

Chart 1.—Findings in Case 3 (M. S.).

effects resulted. The straight lines show the pulse and blood pressure descent in collapse, following exercise of 44,838 foot pounds. In the latter case, M. S. was in competition with another boy, this fact accounting for his greater exertion. The pulse rate drops more quickly in collapse, and the blood pressure exhibits a sudden fall (11 mm. below normal at 120 seconds). The subject was told to bend his head, a drink of water was given to him, and he felt better. The blood pressure rose 10 mm. to drop again 5 mm. below the preexercise level. The normal reading was finally maintained after 390 seconds. When taken off the bicycle, the boy complained of headache.

CASE 4 (Table 4).—F. L., aged 14, a tall boy, felt perfectly well after exercising 24,952 foot pounds. He collapsed, however, after 16,260 foot pounds. In this experiment, signs of collapse did not manifest themselves until 360 seconds after cessation of exercise. At 420 seconds, the blood pressure had dropped 25 mm. below the preexercise level. When asked at 360 seconds whether he felt all right, he did not admit that he was ill; but one minute

TABLE 4.—*Findings in Case 4 (F. L.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
180	...	5	...	147
...	192	10	...	...
168	...	20	146	147
168	...	30	...	149
...	192	40	148	153
156	...	50	...	151
144	168	60	148	147
144	156	90	146	144
144	144	120	143	137
132	144	150	142	136
132	132	180	130	133
132	132	210	128	129
132	108	240	129	127
132	132	270	130	124
132	120	300	124	121
132	120	330	119	120
126	...	360	104	116
126	120	390	...	116
126	120	420	94	115
126	...	450	Collapse	113
132	...	480	...	113
...	...	510	...	...
132	...	540	...	...
...	...	570	...	...
...	...	600	...	...

* Preexercise pulse rate: collapse, 96 beats; normal, 102 beats; preexercise blood pressure: collapse, 119 mm.; normal, 110 mm.

later he compained of severe nausea and therefore was taken off the bicycle. The circulatory reactions after exercise of 24,952 foot pounds were normal. In attempting to explain the discrepancy in Case 4, we found that the boy had a rhinitis and pharyngitis on the day that he rode 16,260 foot pounds, which explains the fact that he collapsed after a smaller amount of work.

CASE 5 (Table 5).—H. G., aged 9, a well developed boy, collapsed after the first experiment, having accomplished 22,905 foot pounds on the bicycle. His blood pressure before exercise was 107 mm. and this level was passed at about 120 seconds after exercise. At 360 seconds, the blood pressure had dropped 15 mm. below normal, to rise to 101 mm. at from 420 to 450 seconds. The last audible reading was 94 mm. at 540 seconds. At 570 seconds, the blood pressure could not be heard at all. Collapse followed, and the child was taken off the bicycle. The blood pressure was still 93 mm. (15 below normal), while the pulse rate had reached its normal level.

CASE 6 (Table 6 and Chart 2).—H. F., aged 15, and of splendid physique, of the 110 children examined for their maximum physical capacity on the ergometer, rode the longest and fastest (123,599 foot pounds). In a previous experiment, he had exercised 68,701 foot pounds, after which his circulatory

TABLE 5.—*Findings in Case 5 (H. G.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	...	5	122	130
...	...	10	128	127
...	...	20	118	127
...	...	30	116	127
...	...	40	115	123
...	...	50	111	...
...	...	60	111	122
144	...	90	113	118
...	...	120	107	113
132	...	150	98	112
...	72	180	...	109
138	...	210	98	111
132	144	240	99	107
...	...	270	...	109
...	144	300	...	107
...	...	330	94	105
132	...	360	92	105
...	138	390	...	...
144	...	420	...	100
138	...	450	101	100
...	126	480	101	101
126	138	510	...	101
...	...	540	94	101
132	...	570	Not audible,	100
...	144	600	collapse	102

* Preexercise pulse rate: collapse, 107 beats; normal, 96 beats; preexercise blood pressure, 107 mm.

TABLE 6.—*Findings in Case 6 (H. F.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
192	192	5	142	...
...	192	10	...	...
...	...	20	...	150
...	156	30	129	...
...	144	40	118	150
...	...	50	118	...
120	138	60	120	150
120	120	90	112	147
108	132	120	105	140
120	120	150	94–85	132
120	120	180	90	127
120	120	210	89	122
120	...	240	Felt faint	119
108	108	270	90	115
108	108	300	90	117
...		330	85; 74	114
...		360	Nauseated, collapse	...
...	Heart sounds	390	..	...
..	dull	420	..	...
...		450	...	...
...		480	...	...
...	108	510	...	...
...	102	540	...	...
...	96	570	...	...
...	96	600	...	...

* Preexercise pulse rate: collapse, 84 beats; normal, 96 beats; preexercise blood pressure, collapse, 114 mm.; normal, 118 mm.

reactions were normal, as can be seen from the dotted lines in Chart 2. Six minutes after the ride of 123,599 foot pounds, however, he completely collapsed. The blood pressure and pulse curves obtained in this instance are typical collapse curves; the continuous precipitate drop of the blood pressure, the sub-

normal phase (40 mm. below normal, the highest subnormal reading obtained in our experiments). The curve to the left of the dividing line, representing the blood pressure readings during exercise, is typical in its slight ascent immediately after the beginning of exercise, forming practically a straight line thereafter throughout the experiment. Typical for collapse is the sudden drop of blood pressure at cessation of exercise, instead of a slight increase of the blood pressure during the first thirty seconds following cessation of work, as is usually the case.

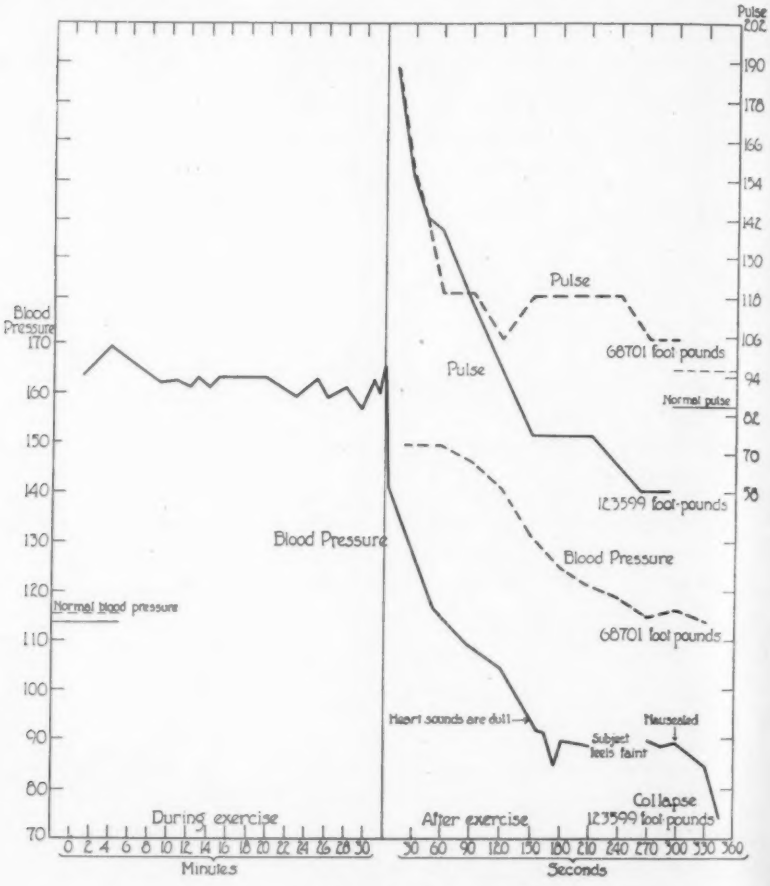

Chart 2.—Findings in Case 6 (H. F.).

CASE 7 (Table 7 and Chart 3).—A. P., aged 13, exhibited a normal course of the circulatory reactions after exercise of 69,354 foot pounds. On repeating the experiment, he was able to ride for but nine minutes, performing 37,040 foot pounds. The maximum rise of the blood pressure in the latter experiment was 28 mm. at five seconds. The blood pressure soon dropped to 119 mm. (at fifty seconds), and reached the preexercise level at about ninety seconds. At 180 seconds, the blood pressure had fallen 19 mm. below normal. The boy complained of nausea and dizziness, and was therefore allowed to lie down. The subsequent readings were taken in the supine posture. Allowing for a difference of 10 mm. between the readings in the lying and standing

TABLE 7.—*Findings in Case 7 (A. P.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	180	5	140	...
180	168	10	140	146
180	156	20	...	...
...	...	30	137	...
168	156	40	...	144
...	156	50	119	...
168	...	60	...	143
144	144	90	111	132
144	144	120	110	130
144	144	150	109	124
144	132	180	96	124
132	132	210	Collapse	125
132	...	240	111	120
138	...	270	107	119
132	...	300	115	118
132	...	330	115	120
132	...	360	117 Taken	118
120	...	390	122 lying	116
132	...	420	...	115
126	...	450	...	116
120	...	480	120	114
...	...	510	...	...
...	...	540	...	...
...	...	570	...	...
...	...	600	...	...

* Preexercise pulse rate: collapse, 80 beats; normal, 106 beats; preexercise blood pressure, collapse, 112 mm.; normal, 114 mm.

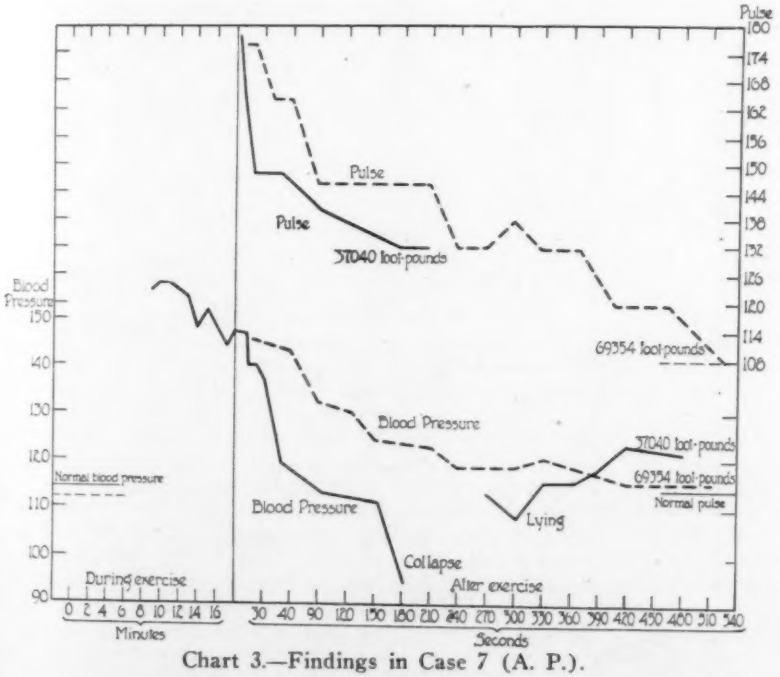

Chart 3.—Findings in Case 7 (A. P.).

TABLE 8.—*Findings in Case 8 (I. B.)*

Pulse *				Blood Pressure		
Normal 2	Normal 1	Collapse	Time, Seconds	Collapse	Normal 1	Normal 2
192	...	168	5	152	...	150
180	168	...	10	152	127	149
168	168	156	20	141	134	152
156	156	...	30	138	133	154
156	156	132	40	137	136	152
156	156	...	50	130	...	156
144	156	132	60	120	136	159
138	...	...	90	...	133	150
126	144	...	120	117	135	145
126	138	108	150	115	130	136
126	138	108	180	Collapse	129	129
126	132	...	210	...	126	133
126	132	..	240	...	120	127
126	144	..	270	...	...	121
126	126	116	300	120	130	129
126	132	...	330	...	129	125
126	132	...	360	...	124	127
120	132	...	390	...	124	127
120	132	...	420	...	119	127
120	132	...	450	...	119	127
120	132	...	480	...	119	...
120	126	...	510	..	119	119
...	126	...	540	...	119	...
...	126	...	570	...	118	...
...	126	...	600	...	119	...

* Preexercise pulse rate, 96 beats; preexercise blood pressure: collapse, 130 mm.; normal, 124 mm.

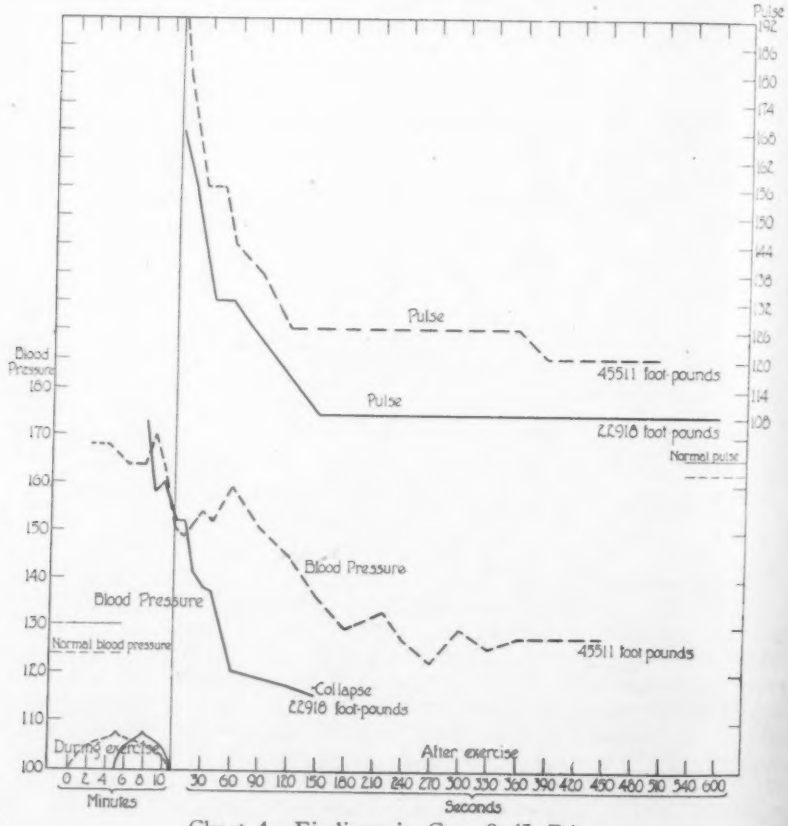

Chart 4.—Findings in Case 8 (I. B.).

position in favor of the lying position, these figures would indicate a return of the blood pressure to normal at about 420 seconds. The boy admitted after the experiment that he was suffering from a sore throat. This may have been the cause of the collapse resulting after only 60 per cent. of the work he was able to perform on a previous occasion without untoward effects. He stayed away from school in the afternoon, and returned in good physical condition the next morning.

Case 8 (Table 8 and Chart 4).—I. B., aged 14, a strong and sturdy boy, who rode the bicycle three times, performed 46,705 foot pounds the first time (Table 8, under Normal 2). The blood pressure curve as well as the pulse curve after cessation of exercise are normal. He developed a murmur at forty seconds. The reaction time was 420 seconds. A month later, on riding the bicycle again, he was able to do 45,511 foot pounds (Table 8, under Normal 1). Except for fatigue, he did not complain of any symptoms of overexertion. The circulatory reactions after exercise were the usual ones. The reaction time of

Table 9.—*Findings in Case 9 (E. B.)*

Pulse *			Blood Pressure	
Collapse 2	Collapse 1	Time, Seconds	Collapse 1	Collapse 2
192	...	5	...	156
180	192	10	...	155
...	...	20	142	153
168	168	30	140	152
156	168	40	...	144
...	...	50	..	134
144	156	60	...	132
144	...	90	118	132
132	120	120	103	115
132		150	Collapse	104
132		180	...	105
132	Heart sounds faint	210	...	101
126		240	...	103
126		270	...	103
126	96	300	..	102
120	...	330	...	Collapse
120	...	360	..	100
116	...	390	...	108
114	...	420	..	109
114	...	450	...	110
114	...	480	..	114
114	...	510	...	106
...	...	540	...	...
106	...	570	...	104
106	..	600	...	100
106	...	13 min.	...	112

* Preexercise pulse rate: collapse 1, 96 beats; collapse 2, 90 beats; preexercise blood pressure: collapse 1, 111 mm.; collapse 2, 113 mm.

the blood pressure was 360 seconds. A week later, he rode the bicycle for the third time. After five minutes' exercise, he asserted that he was unable to continue. He had accomplished only 22,918 foot pounds. The exercise was discontinued, and the circulatory reactions were tested. Typical collapse curves were presented. There was a precipitate drop of the blood pressure, reaching the preexercise level at fifty seconds, and a subnormal phase (from fifty to 150 seconds; the normal blood pressure equaled 130 mm.). The blood pressure could not be observed between 150 seconds (time of collapse) and 270 seconds. A reading taken twelve minutes after cessation of work gave the blood pressure as 117 mm., 13 mm. below the preexercise level. Chart 4 presents fully the circulatory reactions in collapse of subject I. B. His lowered physical capacity was due to a cold (cough), as admitted afterwards.

Case 9 (Table 9).—E. B., aged 15, one of the athletes of the school, who rode the bicycle twice, collapsing each time, in the first experiment rode for twenty-two minutes at a speed of 277 revolutions per minute, performing 101,260 foot pounds. The pulse rate as well as the blood pressure fell precipitatedly after cessation of work, the former reaching the preexercise level

at 300 seconds (an abnormal occurrence); the latter falling 8 mm. below normal at 120 seconds. The readings had to be discontinued on account of collapse. Five weeks later, he insisted on riding the bicycle again in order to outdo H. F. He stopped, however, after nine minutes, having performed but 40,811 foot pounds (as was learned later, he had a cough, and hoarse voice). Here again we find the subnormal phase, with 101 mm. (12 mm. below normal). He felt nauseated and faint at 120 seconds, when the blood pressure had fallen 17 mm. The readings had to be discontinued from 300 to 330 seconds on account of collapse. The last blood pressure taken was 112 mm. (preexercise level) at thirteen minutes.

CASE 10 (Table 10).—D. F., aged 15, of strong constitution, performed 108,762 foot pounds in twenty-four minutes and thirty seconds, without any complaint of ill effects. The circulatory reactions after cessation of exercise were normal. Two weeks later, running a race with H. F., he rode for twenty-seven minutes, at a lower speed, however, than in the previous experiment, thus

TABLE 10.—*Findings in Case 10 (D. F.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
192	180	5	126	142
...	180	10	...	146
180	...	20	...	144
168	...	30	122	143
...	168	40	118	140
156	144	50	...	143
144	144	60	118	141
144	132	90	117	138
144	132	120	109	134
132	132	150	106	128
144	132	180	104	120
132	132	210	102	122
120	120	240	99	114
132	120	270	96	114
132	112	300	96	113
...	120	330	...	113
...	...	360	...	114
...	...	390	...	112
...	112	420	100	...
...	...	450	98	...
...	...	480	90	...
...	...	510	...	...
...	...	540	Nauseated	...
...	...	570	...	...
...	...	600	108	...

* Preexercise pulse rate: collapse, 90 beats; normal, 96 beats; preexercise blood pressure: collapse, 101 mm.; normal, 113 mm.

bringing his work to but 106,208 foot pounds. After exercise of 108,762 foot pounds, the maximum blood pressure rise was 33 mm.; after 106,208 foot pounds, practically the same amount of work, only 25 mm. While in the first experiment the blood pressure was still 21 mm. above normal at 120 seconds, it had already dropped to 109 mm. (18 mm. above normal) in collapse. While in the former the blood pressure maintained itself at the preexercise level from 240 seconds on, in the latter it passed this level at 240 seconds. The boy felt sick at 330 seconds, so that the readings had to be discontinued for the time being. The maximum fall was observed at 480 seconds (11 mm. below normal). No further readings were taken on account of nausea.

CASE 11 (Table 11).—R. B., aged 12, brother of E. B., collapsed after exercising 49,754 foot pounds. The lowest blood pressure reading after cessation of exercise was 19 mm. below the preexercise level. He felt so weak that the blood pressure cuff had to be removed.

CASE 12 (Table 12).—A. G., aged 12, a healthy, well developed boy, brother of H. G., collapsed in the first experiment (36,248 foot pounds). The first blood pressure reading obtained after cessation of exercise was 119 mm. at twenty

seconds (preexercise reading). The blood pressure had already dropped 28 mm. at 150 seconds, when the readings had to be discontinued because of vomiting. The following week, on repeating the experiment, he performed 33,831 foot pounds. The circulatory reactions in this experiment were slightly

TABLE 11.—*Findings in Case 11 (R. B.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	...	5	...	...
...	...	10	...	...
...	...	20	...	...
...	...	30	...	...
168	...	40	...	147
144	...	50	107	151
...	...	60	99	...
144	...	90	...	146
...	...	120	100	...
144	...	150	87	146
156	...	180	...	142
144	...	210	Collapse	137
144	...	240	...	129
144	...	270	...	124
126	...	300	...	124
114	...	330	...	118
120	...	360	...	...
120	...	390	...	...

* Preexercise pulse rate, 108 beats; preexercise blood pressure, collapse, 106 mm.

TABLE 12.—*Findings in Case 12 (A. G.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	...	5	...	137
...	...	10	...	132
...	...	20	119	129
...	...	30	119	135
...	...	40	104	124
...	...	50	113	119
...	...	60	116	119
...	...	90	109	105
...	...	120	109	113
...	...	150	91	...
...	...	180	...	121
...	...	210	...	115
120	...	240	...	115
...	...	270	...	114
...	...	300	...	111
102	...	330	...	112
108	...	360	...	107
...	...	390	...	102
102	...	420	...	111
...	...	450	...	101
...	...	480	...	107
...	...	510	...	...
...	...	540	...	109
...	...	570	...	113
...	...	600	...	113

* Preexercise pulse rate, 87 beats; preexercise blood pressure: collapse, 119 mm.; normal, 110 mm.

irregular, as can be seen in Table 12. This may be due to the fact that he was allowed to drink water and to bend his head to avoid collapse.

COLLAPSE AFTER DUMBBELL EXERCISE

CASE 13 (*a* and *b*).—R. T., aged 13, collapsed after having swung two 4-pound dumbbells from the floor the full arm length 120 times (*a*) and 110 times, (*b*) respectively. He was very dyspneic after the exertion. The circulatory reactions confirmed the findings on the ergometer in the cases of collapse after

exercise. After 120 swings, the blood pressure had risen 5 mm. at ten seconds, to fall 7 mm. below normal at fifty seconds, 28 mm. at 140 seconds, and 44 mm. at 180 seconds. The heart sounds became faint. The readings had to be discontinued on account of great distress. After a short rest, a reading was taken at the end of five minutes, with the boy lying on his back. The blood pressure had returned to normal. Two weeks later, he was asked to swing the dumbbells 110 times. The maximum blood pressure reading after exercise was obtained at forty seconds (14 mm. above normal). The blood pressure curve after exercise took practically the usual course for 150 seconds, reaching the preexercise level at 130 seconds. At 155 seconds, the blood pressure showed a sudden drop of 7 mm. below normal, falling as low as 47 mm. below normal at 310 seconds. The fall in the blood pressure coincided with the physical discomfort experienced by R. T. from 155 seconds on. The readings were discontinued at 310 seconds, on account of nausea.

CASE 14.—C. T., aged 13, a fat boy, had swung two 4-pound dumbbells 100 times without ill effect. The percentage of recovery of the blood pressure at 180 seconds was 92.8; that of the pulse rate, 76.5. Two weeks later, the boy was told to swing two 4-pound dumbbells but thirty-five times. He vomited, 240 seconds after cessation of work. The blood pressure had reached the preexercise level at 120 seconds and had fallen 28 mm. below normal at 180 seconds. The highest drop was obtained at 240 seconds (39 mm.), at which time he vomited. The blood pressure was still 20 mm. below normal, five minutes and thirty seconds after cessation of exercise. When questioned about his physical condition, the boy admitted that he had been suffering from a headache that day and that he felt very tired from playing football during the two weeks of Thanksgiving vacation.

COMMENT

The physiology of muscular exercise is highly complicated. Not only the muscles of the body, but also the heart muscle, the vagus nerve, the vasomotor system, the heat regulating apparatus, the lungs and even the central nervous system are all mobilized in muscular activity. In all of our cases of collapse, two striking facts were observed: 1. Subjective signs resulting from exhaustive exercise simulating those in shock. This suggests a sudden anemia of the brain. 2. A marked drop in the systolic blood pressure and the pulse rate after cessation of exercise in every collapse.

The explanation of the curves obtained must be sought in the cause of the sudden lowering of the blood pressure and the pulse rate. 1. Is the fall of the blood pressure and the pulse rate due to an overstretching of the heart muscle beyond the physiologic limits? At the beginning of exercise, the muscles used squeeze the blood into the veins of the muscles, thus causing an increase of venous pressure. The heart muscle must then dilate in order to accommodate the increased amount of blood received. This dilatation depends on the physiologic condition of the heart muscle, the momentary length of the fibers and the thickness of the walls. The opinion that dilatation of the heart occurs in a normal person during severe exercise was advanced by many great clinicians. They claimed to have found, by percussion, an increase in the transverse diameter of the heart, and a displacement of the heart apex to the left and downward. Schott held the same view, at first

through clinical observations, later confirming it by roentgen-ray studies after exercise.[7] Schott's work is open to criticism because the size of the heart was not observed during exercise. In recent years, the opinion has gained ground that, in a normal person, even during and after most exhaustive exercise, the diastolic volume of the heart does not increase. Hoffman (1902), De La Camp[8] (1902), Moritz[9] (1908) and Williamson[10] (1911) found by means of the orthodiagraph that, in healthy people, severe exercise to the point of exhaustion produced no increase in the transverse diameter of the heart; moreover, the transverse diameter actually decreased. In 1914, Nicolai and Zuntz[11] stated that there was a small increase of the transverse diameter of the heart, averaging 4 mm. during exercise, followed within three seconds after cessation of exercise by a definite decrease. In Williamson's experiments, twenty-nine of a series of thirty-two subjects exhibited a smaller heart after exercise, only three subjects showing an increase in heart size.

In our experiments, there is no evidence for the theory that an acute dilatation of the myocardium is the cause of collapse in normal children. In every case, the apex beat was in its normal position; the transverse diameter of the heart was not increased; the subjective signs described above disappeared in a very short time after cessation of exercise, and the child resumed his school work in a normal condition.

Whether or not these curves can be explained on the basis of a disturbance of the function of the vasomotor system, as is the case in shock, will be more fully considered in the next paper, Part 3 of this series: Roentgen-Ray Studies in Collapse.

SUMMARY AND CONCLUSIONS

1. The circulatory reactions following exhaustive exercise resulting in collapse were studied on fourteen normal boys of school age.

2. In collapse, the curves of the blood pressure and pulse rate after exercise assume the same character in every instance.

3. Race, physical development, height and weight have no bearing on the frequency of collapse.

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7. Schott: Zur acuten Ueberanstrengung des Herzens und deren Behandlung, Verhandl. d. IX Cong. f. inn. Med. zu Wien. **9**:448-477, 1890.

8. De la Camp, O.: Experimentelle Studien über die acute Herzdilation, Ztschr. f. klin. Med. **51**:1-79, 1903-1904.

9. Dietlin and Moritz: Ueber das Verhalten des Herzens nach langandauerndem und ansterengendem Radfahren, München. med. Wchnschr. **55**:489-492, 1908.

10. Williamson, C. S.: Functional Testing of Cardiac Power, Lancet-Clinic **111**:201-206, 1914.

11. Nicolai and Zuntz: Füllung und Entleerung des Herzens bei Ruhe und Arbeit, Berl. klin. Wchnschr. **51**:821-824, 1914.

4. In no instance did signs of collapse occur during exercise.

5. In all but two cases, the maximum rise of blood pressure occurred at the first reading (within the first ten seconds) after exercise.

6. No delayed rises were obtained after exercise.

7. The maximum rise of blood pressure after cessation of exercise averaged 30 mm.

8. In sixteen collapses, the blood pressure passed the preexercise level on an average of 127 seconds (with a maximum of 150 seconds in the case of R. T. [*b*], and a minimum of 35 seconds [R. T., *a*]).

9. The curve of the pulse rate after exercise runs parallel with the curve of the blood pressure, although the drop is not so marked.

CALCIUM AND PHOSPHORUS DETERMINATIONS IN THE BLOOD PLASMA IN RICKETS AND TETANY*

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Primarily, three groups of cases were selected for blood studies: cases (1) of milk rickets; (2) of typical severe rickets, and (3) of active tetany showing rachitic changes. The cases covered prematurely born, full-term, breast-fed and artificially fed infants. The majority of the infants were between 4 and 12 months of age. The calcium and inorganic phosphorus content of the blood plasma was determined before treatment, and in some cases after treatment. The studies were started with a possibility in mind that rickets might be classified into low phosphorus and low calcium groups, and a third intermediate group; and that certain clinical manifestations might be anticipated by a study of the blood in infants.

Howland and Kramer [1] determined the inorganic phosphate of the serum in a series of normal children. They found the concentration to average 5.4 mg. per hundred cubic centimeters, with a minimum of 4 mg. and a maximum of 7.1 mg., the higher values usually being found in the serum of exclusively breast-fed children.

Kramer and Tisdall [2] give the average values of calcium found in normal infants as 10.5 mg. per hundred cubic centimeters of serum. These figures agree with those of other investigators.

Howland and Kramer [3] state that a study of the calcium and phosphorus of the serum in children with rickets and with rickets complicated by tetany leads them to believe that the determining factor in the calcification of the bones is the presence of calcium and phosphorus in

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1. Howland, John, and Kramer, Benjamin: Calcium and Phosphorus in Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

2. Kramer, Benjamin, and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921.

3. Howland, John, and Kramer, Benjamin: Tr. Am. Pediat. Soc. **34**:204, 1922. Briggs, A. P.: J. Biol. Chem. **53**:13 (July) 1922 (a modification of the Bell-Doisy method). Kramer, Benjamin, and Tisdall, F. F.: A Simple Technic for the Determination of Calcium and Magnesium in Small Amounts of Serum, J. Biol. Chem. **47**:475 (Aug.) 1921.

such amounts that the product of their concentration in milligrams per hundred cubic centimeters of serum equals a certain minimal figure, which ranges from 30 to 40. In rickets, they found that the concentration of calcium in the majority of instances is essentially normal; whereas, the phosphorus concentration varies from 0.8 to 3.4 mg. With tetany, on the other hand, the inorganic phosphorus usually approaches normal, varying from 3.6 to 5.8 mg. per hundred cubic centimeters of serum; while the calcium is distinctly lowered. The product of the calcium and phosphorus concentration usually varies from 24 to 31, the low product in tetany being due, in the majority of instances, to a diminution of the calcium concentration. It will be seen that the product in tetany is higher than it is in the many uncomplicated cases of rickets. In other words, it is nearer the healing point, and this is in line with the experience that the evidences of rickets in patients with tetany are not usually of a high grade.

Shipley, Park, McCollum and Simmonds [4] believe that there are two chief types of rickets: one characterized by a normal or nearly normal blood calcium and a low phosphorus (low phosphorus rickets); and the other, by a normal or nearly normal blood phosphorus but a low blood calcium (low calcium rickets). These authors base their views on the experimental production of rickets in rats by various alterations in the diets.

These authors state: "As is well known, tetany complicates certain cases of rickets, but not by any means all. Cases of rickets, even very severe, exist, in which tetany does not supervene. It is with the less severe forms of rickets that tetany usually allies itself." They found that, in some cases of rickets accompanied by tetany, the roentgen ray shows a deposition of lime salts at the cartilage-shaft junctions of the long bones of the extremities; apparently cases of healing rickets. They believe the reason for this is, in many instances, this:

> In the low calcium and the low phosphorus forms of rickets, calcium-phosphate ratios exist in the blood which do not permit at all or permit to only a very limited extent the deposition of calcium and phosphate in the bones. Between the low calcium form of the disease and the normal condition, on the one hand, and the low phosphorus form and the normal condition on the other, are innumerable gradations, presumably characterized by calcium-phosphate ratios in the blood, very probably oscillating ratios which permit calcium phosphate deposition in varying degree, from the most fragmentary to almost complete calcification. In connection with both the low calcium and the low phosphorus forms of rickets, therefore, there are borderline states of the disease in which the calcium-phosphate ratios are such as to permit calcium phosphate deposition to take place irregularly or intermittently in the bones.
>
> According to present knowledge, the relationship between tetany and rickets appears to be as follows: Tetany is an expression on the part of the nervous

4. Shipley, P. G.; Park, E. A.; McCollum, E. V., and Simmonds, Nina: Is There More Than One Kind of Rickets? Am. J. Dis. Child. **23**:91 (Feb.) 1922.

tissues of an insufficiency of the calcium ion; rickets is an expression on the part of the skeleton of disturbed relations between the calcium and phosphate ions of the body fluids. The reason that tetany is so frequently associated with rickets is because rickets is a disease in which the calcium ion in the body tissues and fluids is subject to wide variations. Tetany occurs independently of rickets just as rickets occurs independently of tetany. Since tetany may occur with the low phosphorus form of rickets, it does not serve to mark off one form of rickets from the other. Tetany is essentially associated, however, with the low calcium form of rickets and, for all practical purposes, the low calcium form is the rickets of tetany.

Another interpretation of tetany is that of György, who believes that, notwithstanding the fact that the phosphorus values are rarely above normal, one can speak of a relative phosphorus stasis, and, further, that a phosphate impoverishment of the blood prevails in rickets, while a relative phosphate congestion is found in tetany. György [5] further states that the amount of calcium ions in the serum depends less on the total calcium than on the other ions dissolved in the serum. An increase in the bicarbonate and phosphate, as well as a reduction of the hydrogen ion concentration, produces a reduction of the calcium ions and therefore acts to produce a tetany. These changes indicate an alkalosis of the blood.

Freudenberg and György [6] and Rona and Takahashi [7] believe that there is a tendency to alkalosis in manifest tetany; that calcium ion concentration is directly proportionate to hydrogen ion concentration and inversely proportional to bicarbonate content. They contend that phosphates and bicarbonates may be placed in the same categories—increased phosphorus content tends to diminish calcium ionization. The alkalosis may be neutralized, phosphate diuresis begun and the tetany cured by the administration of hydrochloric acid or of other substances producing an increase of this acid in the body, such as ammonium chlorid and calcium chlorid.

Freudenberg and Aschenheim [8] interpret rickets from a similar standpoint. They found that the blood in rickets is poorer in inorganic phosphate and that the urine of rachitic infants contains more phosphate and excessive amounts of ammonia, both of which are signs of acidosis. The acidosis reduces the phosphate content of the blood as a result of the increased excretion of phosphate in the urine and leads to marked mobilization of calcium, so that the calcium content of the blood remains normal in spite of a protracted loss of calcium; and, in this way, produces an abnormal composition of ions in the blood plasma.

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5. György, P.: Klin. Wchnschr. **69**:1399 (July 8) 1922.
6. Freudenberg, E., and György, P.: München. med. Wchnschr. **69**:422 (March 24) 1922; Jahrb. f. Kinderh. **100**:86, 1922.
7. Rona and Takahashi, quoted from György, P.: Jahrb. f. Kinderh. **99**:1, 1922.
8. Freudenberg, E.: Klin. Wchnschr. **1**:1422 (July 8) 1922. Aschenheim, Eric: Deutsch. med. Wchnschr. **49**:85 (Jan. 19) 1923.

Huldschinsky [9] concludes that tetany is usually associated with the healing stage of rickets and that it is due to the withdrawal of calcium from the body tissues at the time the calcification of the bone is taking place.

MODERATE RICKETS

In a group of eight cases of moderate rickets, we found that the phosphorus was either normal or moderately reduced. Two of these patients had received some breast milk from birth. The calcium in these was normal. In those receiving cow's milk mixtures from birth, there was a moderate calcium reduction. In all of the cases, except one, the product of the milligrams of phosphorus and calcium per hundred cubic centimeters of plasma was over 40.

TABLE 1.—*Moderate Rickets*

Patient	Sex*	Age, Months	Weight Lbs.	Weight Oz.	Race†	Diet	P, Mg. per Hundred C.c.	Ca, Mg. per Hundred C.c.	Remarks
C. B.	♂	7½	9	12	W	Breast and milk mixture from birth	5.4	13.00	Premature; congenital heart thymus; spastic apnea
J. H.	♀	5½	14	..	W	Breast and milk mixture for 4 months	5.56	11.27	Slight rickets
F. R.	♂	7	15	..	W	Breast fed 4 weeks; milk mixture 6 months	4.0	10.35	Little's disease; convulsions since birth
S.	..	3½	12	8	W	Milk mixture from birth	5.23	9.31	
W. B.	♂	4	10	..	W	Milk mixture from birth	4.76	7.54	Spastic paralysis
N. L.	♂	4	13	..	W	Milk mixture	4.76	9.09	
D. B.	♀	13	12	12	W	Milk mixture from birth	3.22	9.40	Full term; microcephalus
A. B.	♂	10	14	..	C	.....	4.50	10.19	

* In this column, ♀ indicates female; ♂, male.
† In the tables, W = white; C = colored.

SEVERE RICKETS

In a group of seventeen cases of severe rickets, all except one case had a phosphorus content below 2.7, ranging as low as 1.35. In the one exception, in an infant, aged 6 months, who had received part breast-feeding from birth, there was a phosphorus content of 3.82. The calcium was normal or only slightly reduced in thirteen cases; while in the remaining four (all in colored infants), the amounts ranged from 6.73 to 8.92. The product in all these cases was under 30, and ranged as low as 9. Two of the patients still presenting all the clinical evidence of severe rickets, but roentgenologic evidence of healing, after two and three months, respectively, on cod liver oil showed a phosphorus and calcium product in the first case of 53, in contrast to a former content of 13.5; and in the second case, a content

9. Huldschinsky, K.: Ztschr. f. Kinderh. **26**:5, 207, 1920.

of 65. Two of the patients, both aged 10 months, presented cases which were complicated by acute severe scurvy. They had, with one exception, the lowest phosphorus values of the group: 1.43 and 1.53; while their plasma calcium content was approximately normal. Two cases of congenital syphilis were among the group, the ages of the patients being 11 and 10 months. The complicating syphilis apparently made no difference as compared with other cases showing the same degree of rickets. In several cases in which there had been repeated

TABLE 2.—*Severe Rickets*

Patient	Sex*	Age, Months	Weight Lbs.	Weight Oz.	Race†	Diet	P, Mg. per Hundred C.c.	Ca, Mg. per Hundred C.c.	Remarks
J. F.	♂	10	8	11	W	Milk mixture from birth	1.43	9.45	Severe scurvy; blood taken March 5
		12	..	..	W	Milk mixture from birth	4.96	10.10	Healed scurvy; blood taken May 8; cod liver oil, 1 tsp. twice a day; orange juice, 1 ounce daily for 2 months
J. P.	♂	10	12	..	W	Milk mixture	1.53	11.53	Severe scurvy
M. M.	♀	8	9	5	W	Milk mixture	2.42	11.99	Premature
E. T.	♂	8	8	8	W	Milk mixture	5.80	11.30	Premature; cod liver oil 3 months
C. F.	♂	17	20	..	C	Breast fed 2 months	1.35	6.73	No cod liver oil
R. A.	♂	11	17	..	W	Breast fed 2 months	2.38	12.17	Congenital syphilis; repeated convulsions from birth
E. S.	♀	6	9	..	C	Eagle brand milk	2.08	10.90	Serum in this case showed: P, 2.5; Ca, 13.1
G. S.	♀	10	12	..	C	Milk mixture	2.00	7.30	No cod liver oil; congenital syphilis
L. R.	♂	8	16	..	C	Breast and milk bixture	2.22	10.72	
A. B.	♂	7	11	..	C	Milk mixture	2.66	10.09	
S.	..	36	..	..	C	Milk mixture	2.10	12.90	
H. G.	♀	9	14	..	C	Breast fed 7 months	2.12	10.78	COC, 10+
H. A.	♂	19	..	..	C	Breast fed 11 months	2.15	8.92	
L.	..	16	..	..	C	Breast fed 1 year	2.12	9.40	Full term; COC, 10+
B. A.	..	..	..	..	C	.....	2.37	7.05	
E. W.	♂	14	15	..	C	Milk mixture from birth	2.12	11.45	Osteopsathyrosis; multiple fractures
J. C.	♂	6	13	8	W	Breast and milk mixture from birth	3.82	10.10	

* In this column, ♀ indicates female; ♂, male.

convulsions, with congenital syphilis and birth hemorrhages as a basis, but in which there was no evidence of tetany, calcium values were approximately normal. One case of osteopsathyrosis with multiple fractures had a phosphorus content of 2.12 and a calcium of 11.45 after six weeks of treatment with cod liver oil.

To summarize, regarding moderate and severe rickets:

1. Clinical signs are of great value in determining the degree of rickets. They are, however, of very little value in differentiating between the active and inactive phases of the disorder.

2. Repeated roentgenologic studies are more important in establishing the active and healing stages.

3. Consecutive blood examinations to determine the phosphorus-calcium concentration and their ratios and products are most important in the diagnosis of the degree and stage of rickets and the prognostication of probable complications.

Definite diagnosis, however, should be based on the three findings mentioned, with relative consideration to past and present diet, environment, season, acute infections and medicinal and physical therapy, since these factors are sufficient in themselves to change, not only the blood findings, but the clinical manifestations as well.

It is believed that calcium and phosphorus concentration with a minimal product between 30 and 40 is the determining factor in the calcification of bones.

All cases of rickets with a calcium and phosphorus content of less than 30 must be considered as in the active zone. The low phosphorus is usually the factor influencing the low product, but this may also be caused by a low calcium, or both.

RICKETS COMPLICATED BY TETANY [10]

In this group of sixteen cases, physical and roentgenologic evidence of rickets was shown in all of them. Six, or 37.5 per cent., were of the severe type, and ten, or 62.5 per cent., were of the moderate type, the diagnosis being based upon the clinical and roentgenologic findings. Four of the severe cases showed definite evidence of healing in the roentgenograms, which was evidently in progress when tetany was superimposed, as, at the time of the blood examination, the calcium averaged 6.3 and the phosphorus 4, with an average product of 25, which is below the value necessary for calcification of bones. Two patients (Cases 3 and 11), aged 11 and 6 months, were still in the florid stage, the product of the calcium and phosphorus being 19.4 and 11.5, respectively. Of ten patients having moderate rickets, eight received breast milk for at least two and one half months, and two were artificially fed from birth. In these ten cases, the phosphorus ranged between 3.3 and 5.6, with an average of 4.4; the calcium between 5.4 and 9.6, with an average of 7.0; while the average product was 31.8. Four cases had a product over 40, and six less than 30. Three of the patients (Cases 9, 11 and 15), aged 5, 6 and 4 months, respectively, were exclusively breast fed. The calcium content in all was below 6. In two patients (Cases 9 and 15), with moderate rickets, the phosphorus was 4.5 and 5.6; in the third (Case 11), with severe rickets, 2.3. The latter breast fed patient, therefore, presented the typical low phosphorus content of severe rickets and the low calcium of tetany.

10. Ten white and six colored infants were studied. Their ages ranged from 4 months to 1 year, with the exception of two, aged 24 and 36 months. Tetany developed in all of them during the months January to May, inclusive.

TABLE 3.—*Rickets and Tetany*

Case	Sex*	Age, Months	Weight Lbs.	Weight Oz.	Race	Diet	P, Mg. per Hundred C.c.	Ca, Mg. per Hundred C.c.	Remarks
1. J. McC.	♂	7	14	10	W	Breast fed 2½ months; milk mixture 4 months	5.3	8.3	Convulsions for 1 week; COC, 4.5; Chvostek, —; craniotabes; moderate rickets
2. M. A.	♀	4½	8	..	W	Milk mixture	4.3	5.4	Premature; COC, 3.0; moderate rickets; latent tetany
3. A. McC.	♂	11	16	8	C	Breast fed 3½ months	4.2	4.64	COC, 2.0; severe rickets; active tetany; convulsions 1 week; laryngeal stridor
		12	..	..	..	.....	2.77	9.72	After 3 to 5 weeks on cod liver oil and calcium
4. J. M.	♀	5	12	..	W	Breast fed 3 months	5.4	7.72	One of twins; moderate rickets; severe tetany; convulsions 2 days; bronchopneumonia; secondary anemia
5. A. F.	♂	36	..	..	W	Breast fed 19 months	4.2	5.09	COC, 2.0; active tetany; moderate rickets; convulsions 2 weeks; laryngeal stridor
6. P. W.	♂	8	27	..	W	Breast fed 5 months, then breast and milk mixture	4.48	6.36	COC, 2.55; spinal fluid increased pressure; moderate rickets; active tetany; convulsions 4 weeks
							4.88	8.27	After 16 days cod liver oil and calcium
7. N. J.	♀	24	..	..	C	Milk mixture	4.89	6.18	COC, 3.0; severe rickets; active tetany; convulsions, 6 weeks
							4.99	7.65	Cod liver oil and calcium 3 weeks
8. E. B.	♀	7	16	..	W	Milk mixture	4.25	5.56	COC, 1.6; moderate rickets; active tetany; convulsions, 4 weeks; carpopedal spasm; secondary anemia
9. D. G.	♀	5	11	8	C	Breast	4.53	5.82	COC, 1.5; severe rickets; active tetany; convulsions 3 weeks; laryngeal stridor
		5½	..	..	..	.....	3.57	11.95	2 weeks, calcium lactate, 15 grains, cod liver oil, 1 dram, 3 times a day
10. M. W.	♀	11	14	..	W	Breast and milk mixture 3 months, then milk mixture	4.73	6.63	COC, 2.0; tetany; moderate rickets; convulsions 1 week
		12	..	..	..	.....	3.97	9.41	COC, 10+; cod liver oil, 1 tsp., twice a day; calcium lactate, 15 grains, 3 times a day; calcium lactate and cod liver oil stopped because of diarrhea 2 weeks before blood was taken
11. P. E.	♂	6	13	..	Gipsy	Breast fed	2.31	5.00	Severe rickets; laryngeal stridor; Chvostek; COC, 3.5
12. D. B.	♀	7	12	5	C	Breast 3 mos.; milk mixture 4 months	3.40	8.10	Active tetany; convulsions for 10 days; COC, 3.0; laryngeal stridor; Chvostek; moderate rickets
13. G. M.	♀	11	18	..	C	Breast fed 3 months	5.60	8.00	Convulsions 3 months; laryngeal stridor; Chvostek ++; COC, 3.5; moderate rickets
14. R. J.	♂	9	15	..	W	Milk mixture	3.34	6.55	Moderate rickets; latent tetany; COC, 4.0
15. A. S.	♂	4	13	..	W	Breast fed	5.60	6.10	COC, 3.0; severe tetany; moderate rickets; convulsions 1 week; never sick before
16. C. N.	♂	11	..	..	C	Breast fed 6 months, then milk mixture	3.33	6.86	Severe rickets; active tetany; COC, 2.5; convulsions 2 days
		11½	..	..	..	Milk mixture	3.34	10.19	Phos. cod liver oil, 1 tsp., 3 times a day; calcium lactate, 30 grains, 3 times a day; COC, 10+
		12	..	..	..	Milk mixture	3.99	11.76	

* In this column, ♀ indicates female; ♂, male.

In five cases treated with cod liver oil, 1 teaspoonful, twice daily, and calcium lactate or chlorid 15 grains (1 gm.), three times daily, for periods covering from two to five weeks, a decided calcium increase was noted, approaching the normal level. In two of the cases, the phosphorus showed a decided decrease, and the remaining three were practically stationary. The two cases showing the marked drop in phosphorus under treatment were of the severe type of rickets. In the first of these, the drop in phosphorus was from 4.2 to 2.7, with a rise in calcium from 4.6 to 9.7; and in the second, the phosphorus decreased from 4.5 to 3.5, and the calcium rose from 5.8 to 11.9.

To summarize, tetany may complicate both moderate and severe cases of rickets.

In every case, the blood calcium was below the normal average. The phosphorus was below normal, but higher than in similar grades of uncomplicated rickets.

The average product of calcium and phosphorus was lower in cases of tetany than in uncomplicated moderate rickets, but slightly higher than in severe rickets.

Although in the majority of our cases there was evidence of healing indicated in the roentgenograms, even in those showing the more severe forms of rickets, the product of calcium and phosphorus was in ten cases below the healing zone.

Although there is a relatively high concentration of phosphorus in cases of severe rickets complicated by tetany, the blood picture tends to revert to the relatively low phosphorus and high calcium content in the early stages of treatment.

The clinical symptoms of tetany improve as the calcium content of the blood increases under treatment and the electrical reactions may be normal even before the calcium returns to the normal figure.

CONCLUSIONS

1. In moderate rickets, the phosphorus or calcium, or both, may be moderately lowered.

2. In severe rickets, the phosphorus is markedly reduced, even in those exclusively breast fed, while the calcium may or may not be lowered.

3. In approximately 40 per cent. of our cases of tetany, severe rickets was present. In rickets complicated by tetany, the calcium is considerably reduced. The phosphorus may or may not be reduced. Under treatment, in the severe cases of rickets complicated by tetany, the phosphorus content at first shows a tendency to decrease or to remain stationary.

4. Our studies have demonstrated that there is a more or less definite blood picture in rickets and in rickets associated with tetany, but we feel that these represent two phases of the same disorder rather than two distinct types, and that the blood picture may be affected by extraneous factors and may vary according to the activity or healing of the process.

A SHADOWGRAPH METHOD OF RECORDING OUTLINES OF HANDS*

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The method here described was devised to make a permanent record of the shape and size of the hands of children. The purpose was to obtain (1) a record on which proportions could be measured for the study of pathologic cases; (2) records for future reference and comparison, and (3) a picture that could be utilized for teaching purposes.

We have found that suitable shadowgraphs can be easily obtained in the following way: The hand is firmly placed with palms down over a sheet of sensitized printing paper (Eastman's "velox"). A 110 volt, 100 watt Edison mazda incandescent lamp is then placed 48 inches directly above the middle axis of the hand, and the sensitized paper is exposed for a period of ten seconds. This procedure should be carried on in a dimly lighted room. The print is then developed with the usual developing and fixing reagents.

The method will be found simple, speedy and inexpensive when compared with drawings, photographs or roentgenograms. As to accuracy, it has been determined that the reproduced image coincides to within 1.5 per cent. of the actual measurements of the hand.

One important precaution should be pointed out in order that an accurate reproduction be obtained: In the cases of infants and very young children, owing to the lack of cooperation, there is a tendency to obtain varying degrees of foreshortening, owing to the fact that the hand and fingers are not in close apposition with the sensitized paper. This can be avoided if sufficient care and patience is observed and if the exposure is made at the opportune time.

The accompanying shadowgraphs illustrate the type of cases on which records of this character are of value for study and for purposes of comparison.

Such records have been obtained in cases of endocrine disturbances, including cretinism and pituitary disease, Mongolian idiocy, pulmonary osteo-arthropathies and Still's disease.

Although the number of cases is not large, the accurate measurements possible enable one to point out and confirm previously existing but indefinite opinions that the relative proportions of the hand of the cretin and the Mongolian idiot show characteristic differences. This may be seen in Figures 2 and 3, which show that although the length of the hands are approximately the same, the length of the palm of

* Received for publication, July 27, 1923.
* From The Childrens Medical Service, Massachusetts General Hospital.

the cretin is less than that of the Mongolian idiot, while the length of the fingers of the former is definitely greater than that of the latter.

These shadowgraphs have proved to be satisfactory as permanent clinical records. They are now being used routinely in the children's

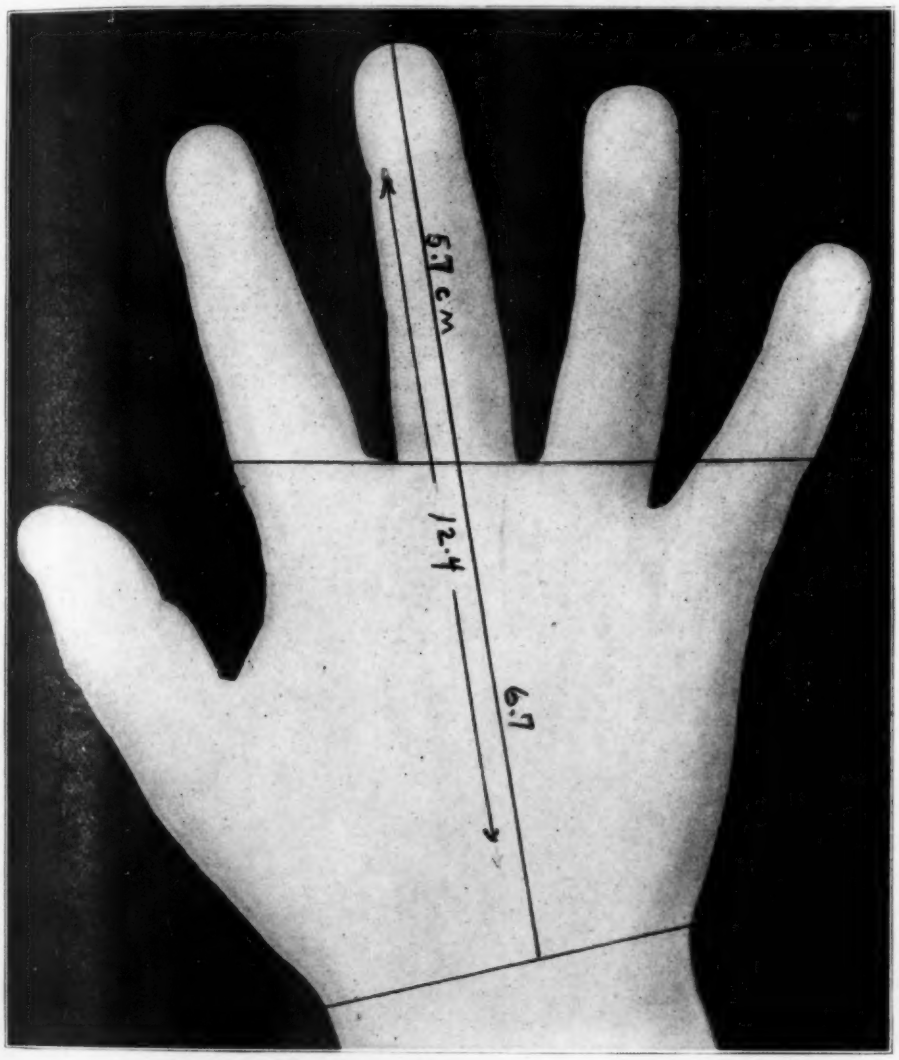

Fig. 1.—Hand of a normal male child, aged 6 years (compare with hand of cretin and Mongol).

medical laboratory of the Massachusetts General Hospital in cases in which a record of growth is desired, and an effect of therapy on abnormalities of shape and proportions might be expected.

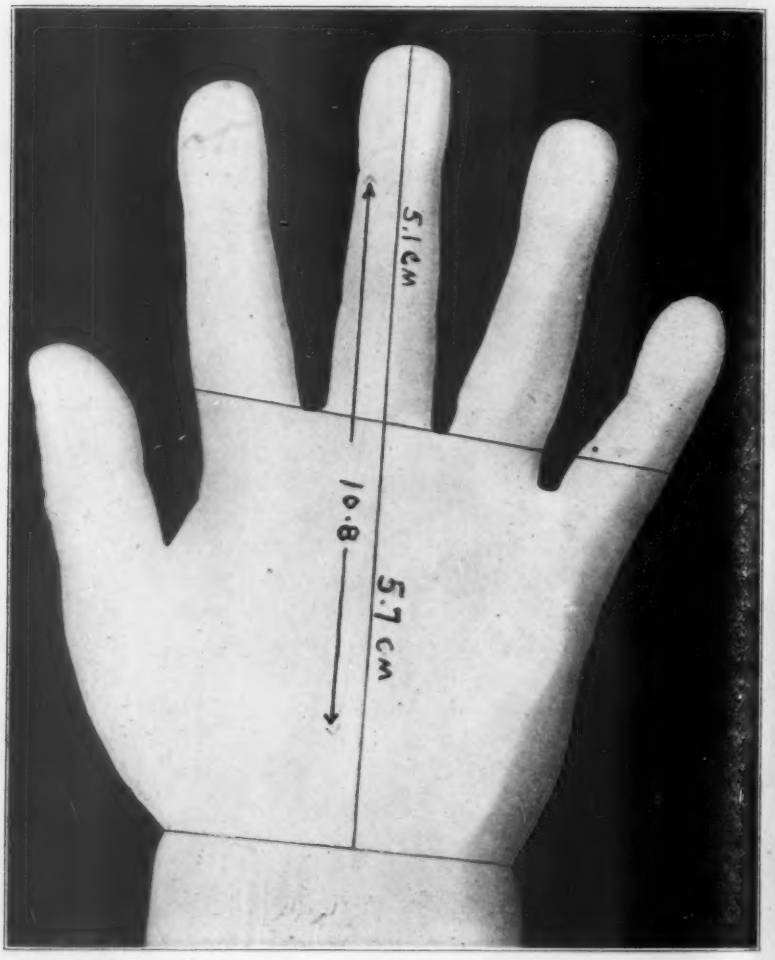

Fig. 2.—Hand of a cretin, a girl, aged 5¾ years. Changes brought in the tissues and skeleton by medication may be compared from time to time.

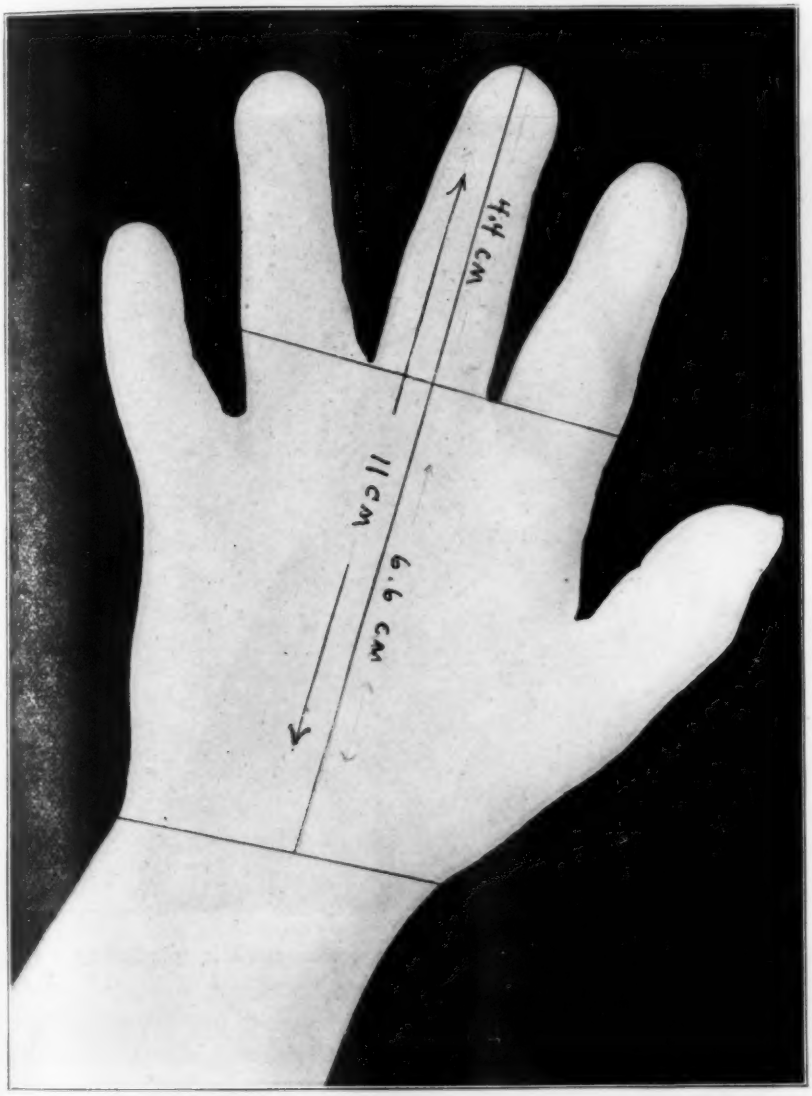

Fig. 3.—The "trident hand" of Mongolian idiocy, that of a girl, aged 6 years. The relative difference between the length of the fingers in this case as compared with those of the normal child and of the cretin should be noted. The hooked little finger is characteristic.

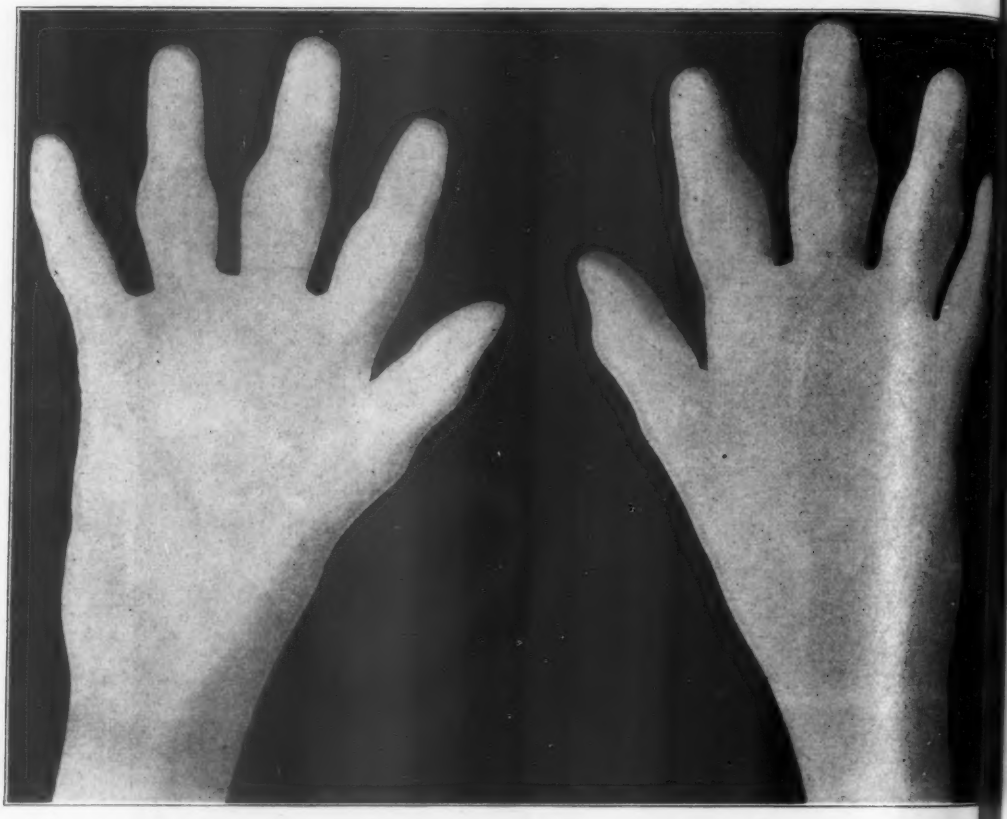

Fig. 4.—Hand of a boy, aged 5 years, showing the characteristic spindleshaped swelling of fingers in arthritis deformans (Still's disease).

RICKETS IN RELATION TO THE INORGANIC PHOSPHATE AND CALCIUM IN MATERNAL AND FETAL BLOOD*

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Whatever may be the conceptions regarding the pathogenesis of rickets, they all concern themselves to some extent with the metabolism of phosphorus and calcium. In infantile rickets, the inorganic phosphorus of the blood is almost regularly diminished; whereas, in tetany —a disorder intimately associated with rickets—the calcium content is diminished. It is becoming increasingly evident that rickets occurs earlier in infancy than was formerly believed: that it is a disorder frequently present in the first half of the first year of life. In Schmorl's statistics, which are based on necropsy findings, 97 per cent. of the infants between the ages of 4 and 6 months showed histologic evidence of rickets. When the matter was viewed in this light, and the possibility that prenatal disturbances of metabolism may play a rôle in the etiology was considered, it seemed worth while to ascertain the calcium and phosphorus content of the blood of the pregnant mother and of her infant at birth, and, furthermore, to follow the welfare of these infants and observe whether there is an association between a diminution of these constituents at birth and the occurrence of rickets during the first year of life. As a preliminary, the blood of a number of pregnant women was tested from the fourth month of pregnancy to term. Table 1 gives the results of these examinations. It will be noted that the average percentage of calcium was 10.4 mg., and that of inorganic phosphorus, 2.77 mg. per hundred cubic centimeters; in other words, that both figures fell well within the normal. Similar results have been reported by other investigators. Lamers [1] found 11.6 mg. per hundred cubic centimeters of calcium in pregnant women, as compared with 10.8 mg. in the nonpregnant. De Wesselow [2] found the calcium somewhat diminished at the eighth and ninth month of pregnancy—9.4 mg.—and the inorganic phosphate normal, 2.72 mg. In tests of cows, Meigs [3] and his associates report the calcium to be unaffected by pregnancy or by lactation.

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* Received for publication, July 18, 1923.
* Read in abstract before the Society of Experimental Biology and Medicine (Proceedings **20**:75, 1922).

1. Lamers, A. J. M.: Ztschr. f. d. ges. Gynäk. u. Geburtsh. **71**:393, 1921.
2. De Wesselow, O. L. D.: Lancet **2**:227 (July 29) 1922.
3. Meigs, E. B.; Blatherwick, N. R., and Cary, C. A.: J. Biol. Chem. **37**:1 (Jan.) 1919.

We next collected blood from the umbilical cord at the time of labor and compared it with the blood of the mother obtained shortly thereafter. For the tests of inorganic phosphate, whole blood was used, diluted with approximately six volumes of water, and without the addition of oxalate or some other anticoagulant. Almost immediately after laking the blood, it was tested by means of the Bell and Doisy method. For calcium serum was estimated by means of Lyman's method. The mother's blood was generally secured within twenty-four hours of labor. Trial tests showed no distinction between the blood of women just previous to labor and that obtained twenty-four or forty-eight hours subsequent to parturition. Table 2 summarizes the results of these comparative tests of inorganic phosphate and calcium of the blood. The outstanding feature is the disparity in inorganic phosphate between mother and infant. The average of the

TABLE 1.—*Phosphorus and Calcium in Blood of Pregnant Women*

Case	Parity	Race	Months Pregnant	Blood: P, Mg. per Hundred C.c.	Blood: Ca, Mg. per Hundred C.c.	Comment
1	7	White	7½	2.64	10.5	
2	2	White	7	2.50	9.5	
3	1	Negro	8	....	11.4	17 years old
4	4	Negro	5½	3.30	12.0	
5	3	White	8	2.64	9.5	
6	2	Negro	8	2.57	10.7	
7	5	White	7½	3.40	10.5	Wassermann reaction +
8	3	Negro	5½	2.72	9.5	
9	3	Negro	8½	2.37	....	
10	7	Negro	4	2.90	....	
11	3	White	7	2.58	10.1	Case 13, Table 2
12	2	Negro	7	2.72	10.4	
13	4	White	6	2.90	10.3	
Average				2.77	10.4	

mothers' blood was 2.89 mg., and that of the infants, 3.71 mg. per hundred cubic centimeters. The significance of these figures lies in the fact that, in all but one instance, the inorganic phosphate of the infant's blood was higher than that of its mother. The calcium estimations require little comment. The average for the infants was somewhat higher than that for the mothers. The figure 9.75 mg. per hundred cubic centimeters for mother's blood is slightly below the normal for adults. There are few estimations of calcium in the serum of the newborn with which to compare our data. Howland and Marriott[4] tested blood from the umbilical cord in three cases, and found an average of about 10.8 mg. Jones and Nye[5] examined the blood of five babies less than 14 hours old, and reported the calcium content as 12.6 mg. per hundred cubic centimeters.

4. Howland, John, and Marriott, W. McKay: Tr. Am. Pediat. Soc. **28**:202, 1916.

5. Jones, M. R., and Nye, L. L.: J. Biol. Chem. **47**:321 (July) 1921.

The inequality of the inorganic phosphorus in the blood of mother and new-born infant requires further comment when one considers the solubility and diffusibility of this salt. The difference in the number of red corpuscles in the blood of the adult and the infant does not furnish an adequate explanation. Zucker and Gutman [6] have shown that the inorganic phosphate is distributed equally between red corpuscles and plasma. Tests which we carried out to elucidate this point further led to the same conclusion: the inorganic phosphate of plasma and of whole blood obtained from the cord did not differ from each other more than 0.2 per cent. As is well known, delay in examination of blood plays an important rôle in estimations for inorganic phosphate,

TABLE 2.—*Phosphorus and Calcium in Blood of New-Born Infants and Their Mothers*

				Mother's Blood		Cord Blood					
Case	Sex*	Parity	Race	P, Mg. %	Ca, Mg. %	P, Mg. %	Ca, Mg. %	Infant's Wt.	Natal Age, Mos.	Duration of Labor Hrs.	Development of Rickets Later
1	♂	3	Negro	3.10	11.0	4.28	11.9	7.3	9	24	Marked
2	♂	3	White	2.72	10.1	4.09	10.2	7.4	9	14½	
3	♀	1	Negro	2.64	9.4	4.09	10.1	6.5	9	17½	Moderate
4	♂	3	Negro	3.35	9.5	3.15†	....	7.1	9	36	None
5	♀	1	White	3.46	9.2	4.50	11.2	5.14	8½	13¼	Slight; nursed 6 months
6	♀	6	Negro	3.00	10.7	3.33	....	8.14	10	6	Moderate; 2 carpal centers at birth
7	♂	2	White	2.81	10.3	3.05	9.2	6.9	9	19¼	
8	♀	3	White	2.70	10.0	3.91	11.4	7.6	9	2	
9	♀	3	White	2.72	9.1	3.75	10.2	7.9	9	3½	Slight
10	♀	3	Negro	3.21	10.0	3.75	11.5	5.2	8	13	Moderate; convulsions
11	♂	3	White	2.57	9.3	4.27	10.6	7.7	9	5¼	
12	♀	3	Negro	2.72	10.3	3.21	12.6	4.13	8	11	
13	♂	3	White	3.15	9.6	4.41	10.6	6.8	10	12½	Slight; Case 12, Table 1
14	♂	4	White	2.81	9.4	3.91	11.4	8.0	9	41	
15	♀	4	White	2.63	9.7	2.90	....	7.0	9	4½	Slight
16	♂	3	White	3.10	9.1	3.33	10.8	8.0	9	..	None
17	♀	4	Negro	2.81	10.0	2.90	9.5	7.11	10	1	Marked; nursed 7 mos.
18	..	2	White	2.50	10.2	3.52	11.0	8.5	9	3½	None
19	♀	2	Negro	2.88	9.4	4.17‡	11.1	...	7	6½	Wassermann ++++; baby died same day
20	♂	5	White	2.76	9.5	4.18	10.9	8.13	9	8½	Slight
21	♀	3	White	3.10	9.7	3.27	9.1	7.8	9	3¼	Toxemia of pregnancy
Average.....				2.89	9.75	3.71	10.75				

* In this column, ♀ represents female; ♂, male.
† Only instance in which mother's blood contained more phosphorus than that of infant.
‡ Premature infant.

leading to a conversion of organic into inorganic phosphorus. Special precaution, therefore, was exercised to carry out the tests as soon as possible after the blood had been shed. In most instances, the interval was not more than from ten to fifteen minutes. It is true that "standing" generally raises the percentage of inorganic phosphate. However, experiments carried out in this laboratory by E. A. Tolstoi showed that the effect of the time factor is variable. Standing for a period of three hours brought about, in some instances, no increase in inorganic

6. Zucker, T. F., and Gutman, M.: Proc. Soc. Exper. Biol. & Med. **20**:133, 1923.

phosphate. Eight hours standing in the refrigerator resulted in an increase from 2.92 to 3.7 mg., and in another from 3.1 to 3.7 mg.

It should be borne in mind, in considering the inequality of inorganic phosphate in the blood of mother and child, that the excretion of phosphorus in the fetus is very slight. Heubner [7] showed that the amniotic fluid, as well as the urine voided by the infant during the first eight hours of life, contains only traces of phosphorus. This indicates the marked difference in the metabolism of inorganic phosphorus between fetal and postnatal life; for, as is well known, during the latter period the loss of this constituent by way of the urine is great. We should also remember that the distribution of blood phosphorus between mother and infant is disturbed in other fractions. Slemons [8] has shown that the fetal blood is comparatively poor in lipoid phosphorus, owing to the impermeability of the placenta for lipoids. It is possible that this diminution is associated with the comparative increase in inorganic phosphate which we have found.

Although the blood of the fetus is definitely richer in inorganic phosphate than is that of the mother, it is poorer in this constituent than that of infants a few months of age. As stated, fetal blood contained an average of 3.71 mg. per hundred cubic centimeters; whereas, the blood of the normal infant contains about 4.5 mg. Since it has been shown that the inorganic phosphate of the blood tends to fall during the winter and spring, and to rise during the summer months, it may be added that these tests were carried out during June and July. In our experience, infants whose blood contains less than about 3.75 mg. per hundred cubic centimeters of inorganic phosphorus generally manifest other evidences of rickets. These new-born infants, although having an inorganic phosphate content within the rachitic zone, showed no clinical evidences of rickets. In many of the cases, roentgenograms of the epiphyses were taken within the first ten days of life, but in no instance were signs of rickets seen. In one case, in which the inorganic phosphate was but 3.33 mg., two carpal centers were present at birth.

Extraneous factors did not seem to be responsible for the percentage of phosphate. It could not be brought into relation with the duration of labor, or the employment of forceps, with the administration of anesthetics or with the vigor of mother or child. Prematurity does not seem to tend to a diminution, if one may judge from the case of a baby born at six and one-half months, whose cord blood contained 4.17 mg. of inorganic phosphate (Table 2); nor does congenital syphilis enter into the question, for in only one instance was the Wasser-

7. Heubner, W.: Arch. f. exper. Path. u. Pharmakol. **62**:253, 1910.
8. Slemons, J. M.: Bull. Johns Hopkins Hosp. **34**:7 (Jan.) 1923.

mann reaction positive. Moreover, it has been our experience that the inorganic phosphate in the blood of syphilitic infants is approximately normal. In fact, this test has been of value in differentiating congenital syphilis from rickets in instances in which the roentgenograms were difficult to interpret.

With these cases as criteria, it was decided to observe whether a relationship would be manifested between the percentage of inorganic phosphate in the blood of the new-born and the subsequent development of rickets during the first year of life. With this object in view, some of the infants were kept under supervision throughout the winter. They were examined and roentgenograms were made in the early spring, when rickets is most prevalent. The results of the roentgenographic examinations of the epiphyses are included in Table 2. With these cases as a basis of comparison, it will be noted that, in four instances, rickets developed in babies which had a particularly high phosphate content at birth: 4.28 mg., 4.09 mg., 4.50 mg. and 4.18 mg. On the other hand, cases with a percentage of 3.15 mg., 3.33 mg. and 3.52 mg. gave no roentgenographic evidence of rickets at the age of about 9 months. It is clear that whatever may be the rôle of prenatal factors in rickets, the percentage of inorganic phosphate at the time of birth is not the determining factor; nor does it indicate whether rickets will subsequently develop. In several cases at the age of 3 or 4 weeks, the inorganic phosphate was found as high as 4.2 mg. or 4.5 mg. per hundred cubic centimeters; which seems to indicate that the percentage is rapidly increased as the result of ingestion of food and the changes in metabolism in the first weeks of life.

SUMMARY

The inorganic phosphate of the blood of pregnant women is approximately normal. The calcium is somewhat diminished at term.

The inorganic phosphate of the blood of the mother is almost invariably lower than that of her infant at birth. This holds true although to a less extent, for the calcium.

The inorganic phosphate of the new-born is generally lower than that of infants 1 month of age or older. However, even when the percentage was within the rachitic range, rickets was not evident by clinical or roentgenographic examination.

No relationship was found between the percentage of inorganic phosphate in the blood of the new-born and the occurrence of rickets during the first year of life.

BOOK REVIEW

ANNALS OF ROENTGENOLOGY. III. DIGESTIVE DISTURBANCES IN INFANTS AND CHILDREN, ROENTGENOGRAPHICALLY CONSIDERED. By CHARLES GILMORE KERLEY, M.D., and LEON THEODORE LE WALD, M.D., New York, Paul B. Hoeber, 1923.

This book concerns an interesting series of cases, well illustrated with roentgenograms and briefly discussed. It is questionable, however, whether the work will be of great value to the pediatrician or to the roentgenologist. One can hardly agree with the authors that ".... the subject is covered fairly completely in the series of cases reported...." The technic of roentgen-ray examination, preparation and the like is well described. There is, however, much irrelevant matter and too much detailed treatment for a book with this title. Also, too much emphasis is placed on so-called "gastroptosis." When the habitus of the individual is taken into consideration, actual ptosis or falling down or sinking down of the stomach (or colon) is rarely found. The roentgen ray is of little value in the diagnosis of chronic appendicitis.

CORRECTION

Dr. Cornelia de Lange has called attention to an error in her article appearing in the July issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN. On page 84, second paragraph, fourth line, the phrase "a liquid in the brain" should read "aliquid in cerebro."